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PINK DISEASE: THE MANIFESTATION IN OLDER CHILDREN AND THE ESTIMATION OF THE BLOOD ADRENALINE CONTENT.

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IN previous communications (Cheek and Stace, 1950; Cheek and Hicks, 1950) it has been shown that so-called pink disease is characterized by a severe electrolyte and water disturbance, and that many of the manifold symptoms of this disease can be simply explained in terms of this disturbance. It was concluded from the evidence presented that an underfunction of the vegetative adrenal mechanism existed and that "stress" was an important factor in the causation of this disease.

In a clinical study it was found that the administration of ordinary salt in mild cases would relieve many of the symptoms, whilst in established cases the administration of desoxycorticosterone acetate as well as the salt would greatly accelerate recovery. In the presence of diarrhœa intravenous therapy was necessary. The speed of recovery depended on the severity of the condition.

In this present paper a study of the manifestations of this disease in older children is reported, together with a study of treatment with salt and desoxycorticosterone acetate. In addition investigations into adrenal medullary function are also presented. Other investigations concerning adrenal cortical functions have recently been concluded (Cheek, Hetzel and Hine, in preparation), and a general review concerning the importance of the adrenal gland in diseases of infancy and childhood has already been published elsewhere (Cheek, 1951).

[1] Work performed with the aid of a grant from the National Health and Medical Research Council.

The Blood Adrenaline Content.

An attempt has been made to gain some information concerning the level of adrenaline in the blood. The chemical method of Shaw (1938) as modified by Raab (1941, 1943) has been used. The method according to Shaw and Raab is suited to give relative values for blood adrenaline content, or at least values which are in relation to adrenaline secretion. It has not been possible to obtain absolute values, as the selective absorption by aluminium hydroxide is not totally specific. Raab discusses in his papers all the interfering substances. The method is very delicate, and satisfactory results can be obtained only if all manipulations and time measurements are executed with every possible accuracy and uniformity. For colorimetric estimation a Coleman universal spectrophotometer, model 11, was used and readings were taken at a wave length of 665$\mu\mu$. One curve constructed once from readings of controls of various adrenaline concentrations was not relied upon, but rather each estimation was accompanied by at least two controls, each of two different adrenaline concentrations, so that a greater accuracy could be obtained. Each adrenaline value given represents the average of two or (generally) three estimations.

Twelve estimations on the same sample of blood on three different days were carried out. The result showed that adrenaline in the protein-free blood filtrate deteriorates, or at least that the values for adrenaline given by this analytical procedure steadily decrease, even if the sample is stored under refrigeration. Four recovery experiments carried out on blood with added adrenaline gave

satisfactory results. In general it was found during experiments with the Shaw-Raab technique that a maximum deviation of a single estimation from the average value on the same sample of blood was *plus* or *minus* 25%. The average deviation of any single estimation from the average value of a series of twelve assays on the same sample was *plus* or *minus* 10%. Experience showed that the blood after venepuncture must be mixed as soon as possible with the trichloracetic acid reagent; if blood was allowed to stand for a mere ten minutes before being mixed with this reagent, the result obtained was only one-third of the value obtained for blood mixed immediately.

With this method it has not been possible to demonstrate any gross alteration in the blood adrenaline content in 18 cases of pink disease (Table III).

Analysis of the Data of Blood Adrenaline Determinations in Normal and Pink Disease Children.

The preliminary analyses on the two groups of data, obtained from normal children and from children with pink disease, reveal in each case a highly significant variance ratio. This may be taken as meaning that the experimental error in the determination of the blood content of adrenaline in one child is very small in comparison with the difference between children in the same group. This lack of homogeneity of children in the same group with respect to their blood adrenaline content is a very undesirable, but unfortunately inescapable, feature of the experiment.

To facilitate computation, the blood adrenaline content means for each child were given equal weight, although some of the means were from three observations and some from only two. In view of the above paragraph it will be realized that inaccuracies introduced by equal weighting will be negligible.

The mean blood adrenaline content of the 18 pink disease children is 170·01 milligamma per millilitre and the standard error 90·52. The corresponding figures for the 24 normal children are 162·18 and 62·60.

The difference of the means, 7·83, is not significant, as demonstrated by the "t-test" with a pooled estimate of variance with 40 D.F. (degrees of freedom).

It is unlikely ($P = 0·05$) that the blood adrenaline content of pink disease children is more than 56 milligamma per millilitre higher than that of normal children. At a more conservative level of probability (0·001) it is unlikely that this difference is greater than 92 milligamma per millilitre.

Reports of Cases.

In the cases presented below evidence is again produced to support the view that there is an electrolyte disturbance which characterizes pink disease. The estimation of the plasma sodium levels was carried out by emission spectrophotometry as described previously (Cheek and Stace, 1950). Examination of results shows that the coefficient of variation is 10%.

Relevant data concerning accurate urine volumes and the chloride excretion are included in these case reports. Estimations of the blood cholesterol content disclose low values.

The effect of intravenous treatment in the presence of diarrhœa (and later in the presence of true infective diarrhœa) and the effect of salt with or without adrenal hormones is illustrated in the study of the case shown in Figure I.

Because of the numerous papers that have appeared lately concerning the important role of ascorbic acid in adrenocortical function, this vitamin has also been used in the régime of treatment.

CASE I.—Maureen W., aged two and a half years, had suffered from an attack of measles at the age of eighteen months. After this she had continued to have very little energy, a poor appetite, and general irritability, with occasional outbursts of rage. Sometimes her hands were cold and she sweated about the head. Three months before examination, the child started to lose weight, and developed a tendency to throw things around and to strike her head against the bed and walls. Her appetite continued to be poor, and her sleep was very disturbed. Her mother stated that she frequently had feverish turns during the day, and that she often fell down and took some time to get onto her feet again and start walking. Constipation was present. She also had a history of frequent colds and a persistently running nose, with frequent attacks of "wheezes in the chest", during which she would have to fight for her breath. These had been diagnosed previously as asthmatic attacks.

On examination of the child some muscle weakness was detected; her tonsils and adenoids were enlarged, and the appearance of her face resembled the so-called "adenoid facies". The weight was 32 pounds. Examination of the blood revealed a plasma sodium content of 295 milligrammes *per centum* and a cell volume of 43. The blood pressure was 130 millimetres of mercury (systolic) and 80 millimetres (diastolic). The pulse rate was 130 per minute.

Two teaspoonfuls of salt (six to eight grammes) were administered daily mixed with food, together with oral administration of 200 milligrammes of ascorbic acid. Ten days later the mother reported that the child was eating and sleeping satisfactorily and had gained 14 ounces in weight. Sweating had ceased, and she had much more energy. All treatment was then stopped for one week, and the child promptly relapsed into her original condition and lost the 14 ounces she had gained. The blood investigations then showed a plasma sodium content of 300 milligrammes *per centum*, a cell volume of 42%, a hæmoglobin value of 13·2 grammes *per centum*, a blood cholesterol content of 110 milligrammes *per centum*, and a plasma protein content of 7·3 grammes *per centum*. The blood pressure was 120 millimetres of mercury (systolic) and 80 millimetres (diastolic). She passed in forty-eight hours 545 millilitres of urine, containing 13·3 grammes of chloride per litre (expressed as sodium chloride) or 7·25 grammes per forty-eight-hour volume.

Treatment was recommenced, and a week later the patient showed a gain of one and a half pounds. After two weeks, although there was no further gain in weight, the child had plenty of energy, sweating had ceased, and sleep was normal. Three weeks later, there was a gain of two pounds four ounces, and the blood pressure had fallen to 90 millimetres of mercury (systolic) and 60 millimetres (diastolic) and the pulse rate to 100 per minute. After four weeks blood examination revealed a plasma sodium content of 315 milligrammes *per centum*, a cell volume of 40%, a hæmoglobin value of 13 grammes *per centum*, and a plasma protein content of 7·2 grammes *per centum*. The forty-eight-hour urine volume had increased to 1540 millilitres.

The condition of this child remained satisfactory and weight continued to increase. In the seventh week an infective cold developed, and there was a loss in weight of half a pound. After recovery from this, her progress continued, and two months after beginning treatment she weighed two stone seven pounds twelve ounces. The mother stated that the child no longer had a "running nose", nor had she had any asthmatic attacks. Salt administration was continued. Six months later the child was still making satisfactory progress and salt administration had been discontinued.

Summary: A child, aged two years and six months, with a history of ill-health for over twelve months following a measles infection, promptly responded to salt treatment. She relapsed when the salt treatment was stopped, then responded once again when it was recommenced and showed a progressive improvement over a period of two months. Allergic manifestations became quiescent.

CASE II.—Josephine K., aged three years, had had an attack of pink disease lasting for six months when fifteen months of age. Her mother considered that the child had never really recovered; she was always tired and subject to temper tantrums in which she "threw things about". "If she runs around for about an hour she comes inside exhausted." Her weight was 46 pounds, but this had fallen by six pounds in the last three months. She ate and slept poorly. During the past year the child had been treated as "a nervous child".

On examination of the patient dark rings were present under the eyes, and muscle tone was poor. Blood investigation revealed a plasma sodium content of 290 milligrammes *per centum*, a cell volume of 45%, a hæmoglobin value of 14 grammes *per centum*, a blood cholesterol content of 70 milligrammes *per centum*, and a plasma protein content of 7·5 grammes *per centum*. The blood pressure was 120 millimetres of mercury (systolic) and 85 millimetres

(diastolic). The forty-eight-hour urinary volume was 640 millilitres, containing 7·1 grammes of chloride, expressed as sodium chloride per litre, or 4·5 grammes per forty-eight-hour specimen. The pulse rate was 130 per minute.

Two teaspoonfuls of salt were administered daily in her food, together with 200 milligrammes of ascorbic acid. Ten days later the mother reported that the child was very much improved; eating and sleeping were satisfactory, and she was no longer irritable or subject to outbursts of rage. Her weight was still only 40 pounds. Three weeks after beginning treatment, she had gained one pound in weight, and her condition was much improved. Colour had returned to her cheeks, and the discoloration beneath the eyes had disappeared. Six weeks after beginning treatment, she was still well, sleeping and eating satisfactorily, with plenty of energy and no outbursts of temper. The mother said that the child was now talking frequently. Her weight was forty-one and a half pounds. Blood examination at this stage revealed a plasma sodium content of 300 milligrammes *per centum*, a cell volume of 38%, a hæmoglobin value of 12 grammes *per centum*, and a plasma protein content of 7·2 grammes *per centum*. The blood pressure was 120 millimetres of mercury (systolic) and 70 millimetres (diastolic), and the forty-eight-hour urinary volume had increased to 1700 millilitres.

Two months after the beginning of treatment her weight had increased to forty-four and a half pounds, and the blood pressure had fallen to 100 millimetres of mercury (systolic) and 60 millimetres (diastolic). Six months later the progress was still satisfactory.

Summary: A child, aged three years, had suffered from pink disease in infancy, and in the mother's opinion had never really fully recovered. When examined, she was losing weight, was bad-tempered, lacked energy, ate and slept poorly, and was liable to psychological outbursts. As a result of treatment with salt and ascorbic acid, normal health was restored.

CASE III.—Mary M., aged two years and three months, became irritable and bad-tempered after a febrile illness. She refused food, flew into fits of temper, and threw things. Sleep was disturbed, and over a period of three weeks her weight fell from 30 pounds to 26 pounds. Constipation developed, together with night sweats. She had very little energy, and the mother said that she was not passing much urine. The duration of illness when she was examined was three weeks. Hypotonia was present. The tonsils were enlarged. Blood examination revealed a plasma sodium content of 300 milligrammes *per centum*, a cell volume of 40%, a hæmoglobin value of 12·8 grammes *per centum*, a blood cholesterol content of 85 milligrammes *per centum*, and a plasma protein content of 7·7 grammes *per centum*. The blood pressure was 110 millimetres of mercury (systolic) and 60 millimetres (diastolic), and the pulse rate was 110 per minute. The forty-eight-hour urinary volume was 500 millilitres with a chloride content of 7·2 grammes per litre expressed as sodium chloride, or 3·6 grammes per forty-eight-hour specimen. The eosinophile cell count was 350 cells per cubic millimetre.

The child was given two teaspoonfuls of salt with her food daily and 200 milligrammes of ascorbic acid. After fourteen days of treatment, she slept and ate normally, was no longer bad-tempered and ran about with normal energy. The forty-eight-hour urinary volume had increased to 1290 millilitres. After a month's treatment her condition was excellent, and there was a gain of three pounds in weight (29 pounds). Blood examination revealed a plasma sodium content of 330 milligrammes *per centum*, a cell volume of 38%, a hæmoglobin value of 12·3 grammes *per centum*, a blood cholesterol content of 100 milligrammes *per centum*, and a plasma protein content of 7·5 grammes *per centum*. The blood pressure was 110 millimetres of mercury (systolic) and 60 millimetres (diastolic) and the pulse rate was 110 per minute. The forty-eight-hour urinary volume was 950 millilitres.

After a further month's treatment, the weight was 31 pounds, and she continued to remain in a satisfactory condition. The daily administration of salt was continued. Six months later her progress was still satisfactory, and the salt administration was discontinued.

Summary: A child, aged two years and three months, after a febrile illness became psychologically altered, with anorexia, loss of weight, constipation, lassitude and sleep disturbance. These symptoms had been in evidence for three weeks. She was restored to normal health with salt treatment.

CASE IV.—Colleen J., aged two years and three months, had developed pink disease at the age of nine months; it had begun while the child was teething, and had lasted until she was eighteen months old. By then she had fully recovered and played normally, with no signs of the disease. Four months later, however, when she was twenty-two months old, whilst she was getting her second-year teeth, she again relapsed. Sleep became poor, and it became necessary to force her to eat. On examination the child was lacking in energy, very nervous and constipated. She was liable to outbursts of temper and had persistent colds with a "running nose". Her mother said that "whenever the child was getting teeth, the pink disease became worse". Her weight was two stone three pounds, and there had been no gain for several months. Muscle weakness was noticeable, and the tonsils were enlarged. Blood examination revealed a plasma sodium content of 290 milligrammes *per centum*, a cell volume of 43%, a hæmoglobin value of 13·9 grammes *per centum*, a blood cholesterol content of 85 milligrammes *per centum*, and a plasma protein content of 7·5 grammes *per centum*. The blood pressure was 120 millimetres of mercury (systolic) and 70 millimetres (diastolic), and the pulse rate was 110 per minute. The eosinophile cell count was 270 cells per cubic millimetre. The forty-eight hour urinary volume was 500 millilitres, with a chloride content of seven grammes expressed as sodium chloride per litre, or 3·5 grammes per forty-eight-hour specimen.

The child was given two teaspoonfuls of salt daily with food and 200 milligrammes of ascorbic acid. A week later the appetite had improved, and she was sleeping well and displayed much more energy. The mother said that the nature of the child had changed and that she would talk and play with other children instead of sitting in the background. Three weeks after beginning treatment the child was well and the weight was two stone four pounds eight ounces.

Blood examination now revealed a plasma sodium content of 315 milligrammes *per centum*, a cell volume of 40%, a hæmoglobin value of 12·8 grammes *per centum*, and a plasma protein content of 7·2 grammes *per centum*. The blood pressure was 100 millimetres of mercury (systolic) and 60 millimetres (diastolic). The forty-eight-hour urinary volume had increased to 1500 millilitres, and complete recovery was maintained with salt and ascorbic acid. The child was quite well six months later, and treatment was stopped.

Summary: A child contracted pink disease at the age of nine months; the condition became quiescent at the age of eighteen months, only to reappear again at the age of twenty-two months. It was the mother's opinion that teething precipitated and exacerbated the condition. Treatment was commenced at the age of two years and three months, and normal health was restored with salt and ascorbic acid treatment.

CASE V.—Edward O., aged two years and ten months, had been ill for three months. He was irritable and bad-tempered, and although he was always tired during the day, he would not sleep at night. His appetite was very poor, and his weight had fallen from twenty-six pounds to twenty-two and a half pounds. The child seemed to prefer salty food, was often thirsty and passed only a small amount of urine. The mother said that the child was very lazy and that his whole nature had changed. Three weeks previously he had developed chickenpox, from which recovery was uneventful. He had been diagnosed as suffering from "failure to thrive", and was sent to hospital for investigation. The mother dated the illness from the time that the child was cutting his second-year teeth. Muscle tone was poor and the tonsils were enlarged. Blood examination revealed a plasma sodium content of 290 milligrammes *per centum*, a cell volume of 42%, a hæmoglobin value of 13·6 grammes *per centum*, a plasma protein content of 6·8 grammes *per centum*, a blood cholesterol content of 100 milligrammes *per centum*, and an eosinophile cell count of 350 cells per cubic millimetre. The blood pressure was 120 millimetres of mercury (systolic) and 90 millimetres (diastolic) and the pulse rate was 110 per minute. The forty-eight-hour urine volume was 530 millilitres with a chloride content of 3·6 grammes expressed as sodium chloride.

The child was given two teaspoonfuls of salt mixed with the food and 200 milligrammes of ascorbic acid daily. After one week's treatment he developed more energy, and the appetite improved a little; but some irritability remained, although sleep improved. Five milligrammes of desoxycorticosterone acetate were injected intramuscularly on alternate days for two weeks, and as a result of this the

TABLE I.
Investigations Before Treatment.[6]

Patient.	Age. (Years.)	Plasma Sodium Content. (Milligrammes *per Centum.*)[1]	Cell Volume. (*per Centum.*)[2]	Hæmoglobin Value. (Grammes *per Centum.*)[3]	Plasma Protein Content. (Grammes *per Centum.*)	Blood Cholesterol Content. (Milligrammes *per Centum.*)[4]	Blood Pressure. (Millimetres of Mercury.)		Forty-eight-hour Urine Volume. (Millilitres.)	Urinary Chloride Excretion. (Grammes of Sodium Chloride per Forty-eight-hour Volume.	Blood Eosinophile Cell Count. (Cells per Cubic Millimetre.)[5]
							Systolic.	Diastolic.			
Maureen W.*	2½	300	42	13·2	7·3	110	120	80	545	7·25	670
Josephine K.	3	290	45	14·0	7·5	70	120	85	640	4·5	600
Mary M.	2½	300	40	12·8	7·7	85	110	60	500	3·6	350
Colleen J.	2½	290	43	13·9	7·5	85	120	70	500	3·5	270
Edward O.	2½	290	41	13·6	6·8	100	120	90	530	3·6	350
Barbara M.	3	280	45	13·6	7·5	85	130	100	350	4·0	900
Trevor T.	5	270	48	15·0	8·0	70	105	75	700	2·9	670
Gaylene T.	2½	260	55	17·0	8·3	95	120	80	720	2·6	500
Jennifer W.	6½	295	43	13·9	7·0	80	120	70	1300	6·5	380

* Child had been given salt and then restricted, one week before these investigations. This possibly accounts for her higher chloride excretion.
[1] Normal: 310 to 360 milligrammes *per centum.*
[2] Normal: 35+5%.
[3] Normal: 11 grammes *per centum.*
[4] Normal: 100 to 200 milligrammes *per centum.*
[5] Normal: 50 to 250 cells per cubic millimetre.
[6] The depression of the plasma sodium level, the degree of hæmoconcentration, and the urinary chloride excretion run parallel with the severity of the clinical condition.

general condition improved considerably with a gain of three pounds in weight. Blood examination now revealed a plasma sodium content of 300 milligrammes *per centum*, a cell volume of 40%, a hæmoglobin value of 13 grammes *per centum*, and a plasma protein content of 7·2 grammes *per centum*. This improved state was then maintained with salt alone. The blood pressure fell to 100 millimetres of mercury (systolic) and 60 millimetres (diastolic). Six months later the child relapsed after having discontinued salt treatment. Improvement once again occurred on return to salt therapy.

Summary: This was a child of two years and ten months, who had had symptoms for three months from the time he was cutting his second-year teeth. He was given salt and vitamin *C* with some improvement, and with added corticosteroid injections his condition became satisfactory. Improvement was maintained with salt alone. Relapse occurred six months later, after discontinuation of salt treatment, but improvement was once again brought about with recourse to salt therapy.

CASE VI.—Barbara M., aged three years, had been losing weight over the past year, during which time she had eaten and slept poorly, and had been bad-tempered and irritable. Night sweating was a feature, and thirst was often complained of. She was very easily fatigued, did not like the hot weather, and had a craving for savoury food. Four months previously her weight had been 25 pounds, but now it was only 22 pounds. There was a history of frequent colds and bronchitis every winter since infancy. On examination of the child no coldness or pinkness of the hands was apparent, but the muscles seemed hypotonic, and the conjunctivæ of the eyes appeared congested. The tonsils were enlarged. Blood examination revealed a plasma sodium content of 280 milligrammes *per centum*, a cell volume of 45%, a hæmoglobin value of 13·6 grammes *per centum*, a blood cholesterol content of 85 milligrammes *per centum*, and a plasma protein content of 7·5 grammes *per centum*. The blood pressure was 130 millimetres of mercury (systolic) and 100 millimetres (diastolic), and the pulse rate was 180 per minute. The forty-eight-hour urinary volume equalled 350 millilitres with a chloride content of 11·5 grammes expressed as sodium chloride per litre, or four grammes per forty-eight-hour specimen.

Two teaspoonfuls of salt together with 200 milligrammes of ascorbic acid were administered daily, the salt being mixed with the food and drink. Injections of desoxycorticosterone acetate (five milligrammes) were given intramuscularly three times a week for the first week. As a result of this treatment sleep improved and the child became less irritable, the mother noting that she had more energy. Eating, however, remained poor.

Daily injections were then given, and a week later the child was eating and sleeping well, no longer sweating, and displaying more energy, though some irritability remained. Daily injections were continued for three weeks, during which time improvement was maintained, the patient eating well and muscular tone improving with the vigour of the child at play. During this period she contracted a cold, which lasted for four days and temporarily depressed the appetite. After three weeks of daily injections she was given injections three times a week. Six weeks after commencing treatment the child was in good condition, with bright eyes and vivacious chatter. There was a gain of two pounds in weight. Blood examination revealed a plasma sodium content of 360 milligrammes *per centum*, a cell volume of 38%, a hæmoglobin value of 12 grammes *per centum*, and a plasma protein content of 7·0 grammes *per*

TABLE II.
Investigations During Treatment.[1]

Patient.	Age. (Years.)	Plasma Sodium Content. (Milligrammes *per Centum.*)	Cell Volume (*per Centum*).	Hæmoglobin Value. (Grammes *per Centum.*)	Plasma Protein Content. (Grammes *per Centum.*)	Forty-eight-hour Urine Volume. (Millilitres.)	Blood Pressure. (Millimetres of Mercury.)	
							Systolic.	Diastolic.
Maureen W.	2½	315	40	13·0	7·2	1540	90	60
Josephine K.	3	300	38	12·0	7·2	1700	100	60
Mary M.	2½	330	38	12·3	7·5	1290	110	60
Colleen J.	2½	315	40	12·8	7·2	1500	100	60
Edward O.	2½	300	40	13·0	7·2	1300	100	60
Barbara M.	3	360	38	12·0	7·0	1200	100	60
Trevor J.	5	335	40	12·0	7·5	1100	90	60
Gaylene T.	2½	340	40	13·5	6·8	1030	100	60
Jennifer W.	6½	305	44	14·3	7·4	2100	110	60

[1] It can be seen that after salt administration only, the plasma sodium level does not greatly rise, nor does the hæmoconcentration greatly alter. This has been found in previous cases and indicates that as long as the loss of sodium from the body is continually made good by salt administration, a satisfactory state is eventually produced and maintained. Desoxycorticosterone acetate by raising the renal threshold for sodium produces a restoration of plasma sodium content hæmodilution, and therefore restoration of blood volume—sodium is thus more rapidly restored to the body.

centum. The blood pressure was 120 millimetres of mercury (systolic) and 60 millimetres (diastolic), and the forty-eight-hour urinary volume was 1200 millilitres.

The child then contracted another cold and again the appetite decreased. This improved again when the cold cleared up. Injections were continued thrice weekly for one month. Throughout this time the condition of the child was satisfactory, except that the nasal discharge was still present, although it was not nearly so frequent or

TABLE III.

Number and Name.	Age.	Blood Adrenaline Content. (Milligamma per Millilitre.)
Pink disease subjects.		
1. Mary M. ..	3 years.	56
2. Sandra W. ..	12 months.	123
3. Darrel E. ..	12 months.	134
4. Janet W. ..	7 months.	134
5. Judith P. ..	3 months.	82
6. Roger W. ..	12 months.	100
7. Wendy O'B. ..	9 months.	243
8. Helen E. ..	12 months.	261
9. Charles W. ..	9 months.	131
10. Hether C. ..	11 months.	109
11. Christine D. ..	9 months.	88
12. David N. ..	12 months.	254
13. Robert I. ..	3 years.	245
14. Beth G.	9 months.	367
15. Robert H. ..	18 months.	309
16. Christine A. ..	9 months.	72
17. Christina C. ..	11 months.	162
18. Josephine C. ..	4 years.	204
Normal subjects.		
1. H.B.	12 months.	280
2. Y.A.	3 years.	287
3. B.L.	18 months.	145
4. W.H.	9 months.	120
5. M.S.	6 months.	174
6. B.S.	8 months.	130
7. B.A.	18 months.	195
8. R.N.	14 months.	167
9. R.B.	3½ years.	159
10. R.R.	12 months.	164
11. T.T.	12 months.	143
12. P.R.	9 months.	201
13. H.W.	12 months.	205
14. M.S.	20 months.	130
15. A.C.	10 months.	116
16. B.D.	11 months.	151
17. D.McL.	12 months.	312
18. L.M.	9 months.	104
19. M.B.	8 months.	96
20. S.S.	6 months.	106
21. F.P.	7 months.	70
22. P.F.	8 months.	180
23. D.B.	3 years.	181
24. N.G.	12 months.	80

persistent. Two months after the beginning of treatment, salt alone was administered, and the child was still quite well. The nasal discharge, however, was still present at times. The blood pressure had fallen to 100 millimetres of mercury (systolic) and 60 millimetres (diastolic), and well-being was maintained with salt alone. Six months later the child was quite well, and salt therapy was discontinued.

Summary: This child was aged three years and had a history of ill health extending over one year. She ate and slept poorly, was bad-tempered, and when examined was losing weight. She was often tired, did not like the hot weather and had a craving for savoury foods. With salt and corticosteroid treatment she quickly showed improvement, and after two months well-being was maintained by salt therapy alone.

CASE VII.—Trevor J., aged five years, had developed pink disease at five months of age, when the teeth first started to appear. Since then the child had never thrived as other children, and he always had a cold or some infection. At two years of age the tonsils and adenoids had been removed with some relief for a time. The child had always been irritable, bad-tempered and very nervous, and his appetite and sleeping had been poor. The year before he came under observation he had lost a lot of hair. He was now constipated and often sweated at night. He still had a persistent discharge from his nose and was subject to infections such as colds and bronchitis every winter, with attacks of "wheezes in the chest" which had been diagnosed as asthma. The mother said that he was a very nervous child, easily tired, and that the hot weather was not well tolerated. Four months previously the weight had been two stone ten pounds, but now it was only two stone eight pounds.

On examination the child had poor muscle tone and dark rings under his eyes. Blood examination revealed a plasma sodium content of 270 milligrammes *per centum*, a cell volume of 48%, a hæmoglobin value of 15 grammes *per centum*, a blood cholesterol content of 70 milligrammes *per centum*, and a plasma protein content of eight grammes *per centum*. The blood pressure was 105 millimetres of mercury (systolic) and 75 millimetres (diastolic), and the pulse rate was 100 per minute. The forty-eight-hour urinary volume equalled 700 millilitres with a chloride content of 4·1 grammes expressed as sodium chloride per litre, or 2·9 grammes per forty-eight-hour specimen.

The child was given two teaspoonfuls of salt with his food and 200 milligrammes of ascorbic acid. After two weeks the mother reported that he was eating and sleeping better, and he had gained one pound in weight. The blood examination now showed a cell volume of 40% and a hæmoglobin value of 12·8 grammes *per centum*. He was given daily intramuscular injections of five milligrammes of desoxycorticosterone acetate. A week after the beginning of the injections, and three weeks after the beginning of treatment, the child was eating and sleeping satisfactorily, showed plenty of energy and had lost the dark rings under his eyes. Blood investigation now showed a plasma sodium content of 335 milligrammes *per centum*, a cell volume of 40%, a hæmoglobin value of 12 grammes *per centum*, and a plasma protein content of 7·5 grammes *per centum*. The blood pressure was 110 millimetres of mercury (systolic) and 60 millimetres (diastolic), and the forty-eight-hour urine volume had increased to 1110 millilitres.

Injections were given daily for two weeks. The condition of the child remained excellent, and he gained two pounds in weight. Injections were then given on alternate days for one week, and then the child was given salt alone. The blood pressure fell to 90 millimetres of mercury (systolic) and 60 millimetres (diastolic). After three weeks of salt therapy alone his condition was not so good as when he was having the corticosteroid injections. He still had outbursts of temper, and the appetite had slightly deteriorated. A "Crystule" injection of 50 milligrammes of desoxycorticosterone acetate was given (effective duration one month) with good results. This child was perfectly well six months later, and the salt administration was then discontinued.

Summary: A child, aged five years, with an early history of pink disease at the age of five months, showed failure to thrive for a period of years. He slept and ate poorly, failed to gain weight satisfactorily, was often bad-tempered and liable to outbursts of rage, and had frequent infections, colds and bronchitis every winter, with mild attacks of asthma. Blood examination showed quite a considerable electrolyte disturbance. Treatment with salt and desoxycorticosterone acetate, together with ascorbic acid, was given with relief of symptoms and an alleviation of allergic manifestations. He continued to do well on salt alone for a short time; then the appetite deteriorated a little, and he had some psychological outbursts. He was maintained in good condition by a "Crystule" implant[1] (one month effective duration). He had been regarded by medical opinion as a "nervous child" and as suffering from "failure to thrive".

CASE VIII.[2]—Gaylene T., aged two years and six months, was a premature baby who had never progressed satisfactorily. At three months of age she was admitted to hospital as a subject of "failure to thrive", and at nine months she was discharged from hospital, still underweight. She made rapid progress and at twelve months weighed 28 pounds. She then contracted measles and never really thrived after this infection: there was no gain in weight during the subsequent eighteen months, the appetite was always poor, and the sleep was very disturbed. She also suffered from irritability, bad temper, lassitude and constipation. She was able to run around in the mornings, but was always tired by the afternoon. She showed a preference for salty foods (refusing chocolates and sweets), did not tolerate the hot weather well, and sweated sometimes at night. Recently she had evinced a tendency to fall. She had been diagnosed as a "nervous child" and a subject of "failure to thrive". When examined the child

[1] CIBA, Limited.

[2] Clinical data with photographs relating to this case have been published elsewhere. *Vide* Selye, H. (1950).

weighed 26 pounds. Her hands and feet had always appeared and felt normal, and no allergic manifestations had ever been present. Dark rings were present under the eyes. Her tonsils were enlargd. Muscle hypotonia was pronounced. Blood examination showed a plasma sodium content of 260 milligrammes *per centum*, a cell volume of 55%, a hæmoglobin value of 17 grammes *per centum*, a blood cholesterol content of 95 milligrammes *per centum*, a plasma protein content of 8·3 grammes *per centum*, and a non-fasting blood sugar level of 80 milligrammes *per centum*. The blood pressure was 120 millimetres of mercury (systolic) and 80 millimetres (diastolic), and the pulse rate was 120 per minute. The forty-eight-hour urine volume was 720 millilitres, and the chloride excretion expressed as sodium chloride equalled 3·6 grammes per litre, or 2·6 grammes per forty-eight-hour specimen.

Two teaspoonfuls of salt were given daily with the food together with 200 milligrammes of ascorbic acid. After fourteen days' treatment the child was eating and sleeping a little better, but otherwise there was no improvement. After three weeks of salt treatment no further improvement had occurred; five milligrammes of desoxycorticosterone acetate were then given daily by intramuscular injection. A week later the mother said that the child was beginning to be more active. Blood examination then showed a plasma sodium content of 340 milligrammes *per centum*, a cell volume of 40%, a hæmoglobin value of 13·5 grammes *per centum*, and a plasma protein content of 6·8 grammes *per centum* (albumin 4·9 grammes, globulin 1·9 grammes). The non-fasting blood sugar level was 100 milligrammes *per centum*. The blood pressure was 110 millimetres of mercury (systolic) and 70 millimetres (diastolic), and the forty-eight-hour urinary volume had increased to 1030 millilitres.

A fortnight after the beginning of daily injections (five weeks after the beginning of treatment) the appearance of the child had changed, her eyes appeared clear and bright, and the shadows under them had disappeared. Blood examination now showed a plasma sodium content of 250 milligrammes *per centum*, a cell volume of 41%, a hæmoglobin value of 13·3 grammes *per centum*, and a plasma protein content of 7·5 grammes *per centum*.

Owing to the fact that the mother of this child was a psychiatric patient, the child was admitted to hospital for adequate care and further observation. The child showed a gain of half a pound in weight at the end of the first week in hospital (the sixth week of treatment). She was eating and sleeping well, showed plenty of energy, and ran around most of the day, with no signs of irritability or bad temper. Her muscles had become firm, and she was talking frequently. At the end of the seventh week of treatment her weight had increased to 28 pounds, she had developed colour in her cheeks, and her muscles were firm on palpation. The blood pressure was 100 millimetres of mercury (systolic) and 70 millimetres (diastolic). For the next fortnight the condition of the child remained excellent, and she gained a further half pound in weight. The blood pressure remained constant. She was then given (nine weeks after the start of treatment) a "Crystule" injection of 25 milligrammes of desoxycorticosterone acetate intramuscularly (effective duration of about two weeks) and discharged from hospital. She remained well, and during the next week gained a further two pounds in weight (thirty-one and a half pounds). A week later the blood pressure was 100 millimetres of mercury (systolic) and 60 millimetres (diastolic), and a month later she was still well and happy. She had gained a total of nine pounds in weight. Salt therapy was continued for a further six months, after which it was discontinued because the child was well.

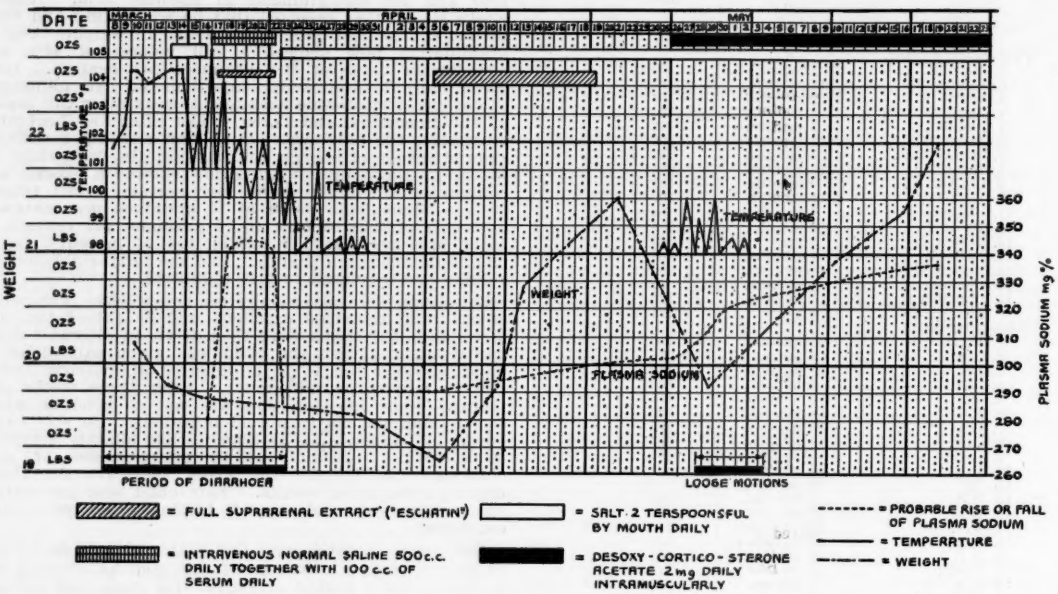

FIGURE I.

Chart from a child, aged ten months, who was admitted to hospital with pink disease, severe diarrhœa and pyrexia; repeated and extensive investigations revealed no infective cause for the pyrexia or diarrhœa. Salt given with the food, two teaspoonsful daily for three days, and one injection of desoxycorticosterone acetate had no effect. The child became comatose and moribund. The intravenous administration of normal saline and plasma restored the child. Cell volume estimations in this case were of no value in determining the degree of hæmoconcentration, as a concomitant anæmia was also present; this also prevented a rough calculation of the true plasma protein level which would have been obtained without the presence of hæmoconcentration. The reticulocyte counts were 11%, 15% and 3·8% on subsequent occasions. Following the pyrexia a continued failure of response is shown in respect to weight with salt alone. The effects of full suprarenal extract and desoxycorticosterone acetate are shown; before and after the giving of "extract" a flat blood sugar curve was obtained. During the eight weeks in hospital the child developed some relaxed green motions, and *Shigella sonnei* was grown from the fæces. This organism had been present in other patients in this ward and in other wards of the hospital, and also amongst the nursing staff at the time.

Summary: The child was aged two years and six months when first examined. She had been a premature baby and had never thrived during early infancy. In spite of this, at twelve months of age she had been well and weighed 28 pounds. After a measles infection she showed a progressive failure to thrive. She gained no weight (and was actually losing when first examined), ate poorly, slept badly, and psychologically was an abnormal child.

She had tiredness in the afternoons, and her legs would give way when she ran about. She had a craving for savoury and refused sweet foods. She was intolerant of hot weather. Investigation showed a severe electrolyte disturbance, which responded only slightly to three weeks' salt treatment. After the giving of five milligrammes of corticosteroid daily for a further three weeks the condition of the child became normal. The physical and mental changes were quite dramatic; she became to all intents and purposes a normal child. She was then given two milligrammes of steroid by single injections, and 25 milligrammes by "Crystule" injection, for a further four weeks, which maintained her in an excellent condition, and she gained weight rapidly (nine pounds). She continued to do well with salt therapy alone.

CASE IX.—Jennifer W., aged six years and nine months, was first seen more than a year ago before investigation into the nature of this disease had begun. At that time she had been admitted to hospital with a history of left-sided pleurisy, and it had become apparent in hospital that she was suffering from "florid pink disease" at five and a half years of age. From this point of view her case was thought to be very unusual and was therefore reported (Cheek, 1949). As was described in that paper, she had a typical rash, profuse sweating with a "mousy odour", and slight or no photophobia. The extremities were red, cold, œdematous and peeling, and she complained of burning pains in them. There was also pronounced hypotonia and tachycardia, and the blood pressure was 150 millimetres of mercury (systolic) and 100 millimetres (diastolic). There were left-sided pleurisy and pneumonia complicating the pink disease. Her weight was forty-one and a half pounds, and the red blood cell count was 6,000,000 per cubic millimetre.

In the year or so after this attack of pink disease and pneumonia, she had an attack of chickenpox. In addition, although she had been subject to frequent colds for most of her life, she had for the whole year a particularly persistent productive cough. A bronchogram, which was prepared four months before she again came under my observation, had revealed bronchiectatic changes in the lower lobe of the left lung and, to a lesser extent, in the lower lobe of the right lung. The mother stated that the child was not very energetic, and was always tired by the afternoon. Her appetite and sleep were poor, and, although her weight had fluctuated a little, she still weighed only forty-one and a half pounds, the same as twelve months previously (when she had had pink disease). Clinical examination showed slight clubbing of the fingers; and X-ray examination revealed an infected left mastoid.

Blood investigations revealed a plasma sodium content of 295 milligrammes *per centum*, a cell volume of 43%, a hæmoglobin value of 13·9 grammes *per centum*, a blood cholesterol content of 80 milligrammes *per centum*, a plasma protein content of 7·0 grammes *per centum*, and an eosinophile cell count of 380 cells per cubic millimetre. The blood pressure was 120 millimetres of mercury (systolic) and 70 millimetres (diastolic). The forty-eight-hour urinary volume was 1300 millilitres, with a chloride content of 4·9 grammes expressed as sodium chloride per litre, or 6·5 grammes per forty-eight-hour specimen.

She was given two teaspoonfuls of salt daily mixed with her food and 200 milligrammes of ascorbic acid daily. After two weeks her appetite improved, her energy improved, and sleep became satisfactory. A healthy colour returned to her cheeks. The blood investigations then showed a plasma sodium content of 305 milligrammes *per centum*, a cell volume of 44%, a hæmoglobin value of 14·3 grammes *per centum*, and a plasma protein content of 7·4 grammes *per centum*. The urine volume increased to 2100 millilitres in forty-eight hours. It was intended that the left mastoid should be operated on. Accordingly, the child was admitted to hospital and given two milligrammes of desoxycorticosterone acetate by intramuscular injection daily, in addition to the other treatment, so that she would be in a satisfactory condition for operation. Aerosol penicillin was also given for the bronchiectasis. As a result of this treatment the child ate and slept well, developed a normal amount of energy, and gained weight. This improved condition was maintained, and six months later satisfactory progress had been made.

In the light of present knowledge this case was very unusual in that the child manifested the "florid" form of pink disease at the age of five and a half years. Whether or not this was the first precipitation of an electrolyte disturbance it is hard to judge, but in my opinion it was present beforehand; the pleurisy and pneumonia merely exacerbated the "stress" and gave rise to the florid condition (compare the case referred to later, that of Anne D.). It is readily understandable that with the failure to thrive which runs parallel with the electrolyte disturbance the frequent respiratory infections which accompany it sometimes produce a state of bronchiectasis.

After salt treatment the child improved greatly. It is interesting that the cell volume and hæmoglobin estimation are increased after salt treatment. This is probably due to the improvement in the general condition. The increased food intake would also effect an amelioration of any associated anæmia. Cell volume estimations do not always give an accurate picture of the hæmoconcentration owing to a coexistence of a malnutritional anæmia. The plasma sodium level alone discloses the true state of affairs.

From a follow-up study of cases of infantile pink disease or infantile acrodynia previously reported (Cheek and Hicks, 1950) it has become apparent that these children have all remained well and that the administration of extra salt is no longer necessary except in the case of two older children mentioned in that paper—Gillian C. and Anne D. If one refers to this previous communication it will be seen that the preceding history of both these children was of long duration (eight months in the case of Gillian C. and several years in the case of Anne D.). The administration of extra salt, two teaspoonfuls daily, has been continually necessary to maintain a state of health in these two children.

Gillian C., aged two years and nine months, has continued to do well over the last six months with treatment (salt only). She has gained 12 pounds in weight and is a normal child. She no longer has frequent colds or infections. Recently, on the stopping of salt therapy the appetite deteriorated, sleep became poor, and she began to sweat at night. The symptoms ceased again when salt therapy was restarted. Reinvestigation of the blood disclosed a plasma sodium content of 295 milligrammes *per centum*, a cell volume of 41%, a hæmoglobin value of 12·5 grammes *per centum*, a blood cholesterol content of 95 milligrammes *per centum*, and a plasma protein content of seven grammes *per centum*. The blood pressure was 110 millimetres of mercury (systolic) and 60 millimetres (diastolic).

Anne D., aged four years and six months, at the age of eight months had suffered from an attack of pink disease, which was severe and lasted for one year. Indeed, in the mother's opinion, the child had never really recovered. At the age of three years and nine months, after chickenpox and pneumonia, she had had a "return" of pink disease (in my opinion an exacerbation), which had been accompanied and followed by frequent asthmatic attacks. Six months after the beginning of treatment she was very well and had gained weight satisfactorily. In the mother's opinion she was a different child—"much healthier and no longer subject to so many colds". She had had no further asthmatic attacks. Reinvestigation of the blood while she was receiving salt therapy showed a plasma sodium content of 305 milligrammes *per centum*, a cell volume of 42%, a hæmoglobin value of 13·3 grammes *per centum*, a blood cholesterol content of 75 milligrammes *per centum*, and a plasma protein content of 7·8 grammes *per centum*. The blood pressure was 100 millimetres of mercury (systolic) and 60 millimetres (diastolic), and the pulse rate was 100 per minute. One week after these investigations the child contracted whooping-cough, and this was ushered in by an asthmatic attack, the first for six months.

Conclusions from the Clinical Study of Cases.

These cases have specifically been chosen because most of them show none of the bizarre symptoms of classical infantile pink disease, which seems to be a more acute, severe, yet often less prolonged disturbance. The delicate skin of the infant readily reveals hæmoconcentration and probably an altered state of the capillaries. In the present cases it is apparent that photophobia, the characteristic changes in the extremities, skin rashes, and profuse sweating are less noticeable. In all these cases, with the exception of two, the patients have a duration of illness extending over at least one year, and in some cases several years; they manifest a failure to eat and sleep well, a lack of energy, a psychological disturbance, and a failure to gain weight, often with concomitant allergic manifestations.

It is not surprising, therefore, that several of these cases have previously been regarded as examples of the "nervous child syndrome", as "failure to thrive", or as "behaviour problems". The evidence, however, points to the possibility that a substantial proportion of children regarded as having the "nervous child" syndrome (Cameron, 1919) or as suffering from "athrepsia" may on investigation exhibit the same underlying electrolyte disturbance, especially if the duration of such an illness is dated from some period of infection or stress.

Rocaz (1936) talked of the "*forme nerveuse*" or "nervous type" of this disease and stated that he believed that it could occur without any change in the extremities or any rash. It has already been pointed out in a previous paper (Cheek and Stace, 1950) that the figures given for the age incidence of pink disease in England, Australia and America do not correspond with those from France. Cosmi (1930) and Rocaz (1933) each found that more than half of their series of cases were in children over two years of age. This relationship also holds in Switzerland (Zwelleger[1]).

From a study of some seventy cases of pink disease occurring in infants and older children who were treated with salt (eight grammes approximately), with or without desoxycorticosterone acetate, it has become apparent that the majority of infants after recovery from pink disease do not require the continued administration of salt. Some, however, are left with a persistent electrolyte disturbance, and as a result of this there develops a type of "nervous child", or sufferer from chronic pink disease. This chronic state of electrolyte imbalance may in the normal course of events be present throughout some years of childhood. It seems that this state of affairs is somehow related to, and exacerbated by, any state of stress—an infection such as "measles", or a non-infective stimulus such as teething, a diphtheria injection, or the mercury poisoning claimed by other authors[2] as a cause.

Hence to maintain the child in an improved state it may well be necessary in such cases to administer added salt to the diet for many months. During this time the child is much more vulnerable to intercurrent infections, and also has a tendency to allergic manifestations. With a mild electrolyte disturbance (plasma sodium level 300 milligrammes *per centum*) recourse to salt alone (even though it does not restore normal plasma sodium levels—see Table II) is satisfactory, but in more severe cases desoxycorticosterone acetate given by intramuscular injection is necessary to restore and maintain for a period the normal electrolyte balance. In these older children the relief of symptoms with treatment has been more complete and more striking than in the younger children, although, as already stated, treatment may have to be continued for a considerable time. With this treatment for infants I have found that steroid injections for a period of from three to six weeks are nearly always necessary and beneficial.

It was noticed previously also that in well-established cases of pink disease the chloride excretion was low (although higher in the early stages) (Cheek and Hicks, 1950). In the present chronic cases, with the exception of two, the children have had a duration of illness over one year and have had a low chloride excretion and low forty-eight hour urinary volume (*vide* Table I).

Discussion and General Conclusions.

Feer (1923) was the first to emphasize that a possible overaction of the sympathetic nervous system existed in pink disease, and many others have supported this view that the hypertension, tachycardia, sweating and occasional hyperglycæmia provided evidence of such a disturbance. Stolz (1926) and also Albertini (1935) (cited by Glanzmann, 1937) claimed to have found hyperplasia of the chromaffin system. Blackfan and McKhann (1933) noted that the pulse rates of patients with acrodynia differed from those of normal subjects in that they did not vary with crying or during sleep. Day *et alii* (1939) measured the electrical impulse of the heart beat with a special recording device. They noticed the effect on the heart rate produced by changes in emotion and following the injection of the drugs atropine, adrenaline, ergotamine tartrate, and mecholyl. These authors reached the conclusion that emotional disturbances failed to evoke certain normal responses from the vegetative nervous system in pink disease. They thought that this failure of the sympathetico-adrenal response to emotion could well arise from the fact that the sympathetic nervous system in a patient with acrodynia might already be overstimulated to such an extent that it could no longer react to further stimulation. It was suggested that a possible similarity existed between children with infantile acrodynia and subjects of pheochromocytoma, although an alternative view was also taken that the hypertension and tachycardia possibly resulted from widespread vasoconstriction due to some obscure toxin.

Glanzmann (1937 and 1948) also suggested that the adrenal medulla produced an increased secretion of adrenaline in pink disease. He investigated this by noting the changes in the iris of an enucleated frog's eye which had been placed in Ringer's solution, to which had been added plasma samples from patients with pink disease. These plasma samples were found to have a strong mydriatic effect, detectable even in a dilution of one in a million. No effect was found with plasma samples from normal children. Glanzmann suggested that a raised blood adrenaline level was responsible for these effects.

It is obvious, therefore, that the methods adopted up to date have been inadequate and incomplete and that some more direct method is necessary to throw greater light on the state of sympathetico-adrenal function. The method used here, although leaving a lot to be desired, has at least shown that the probability is small that there is a rise in the blood adrenaline level.

The low level of the plasma sodium is a characteristic finding in pink disease. This base makes up 94% of the effective osmotic base of extracellular fluid, since the osmotic value of extracellular fluid is almost entirely composed of the sum of the concentrations of its ionic components. Nearly all the plasma base is sodium, so that the integrity of plasma osmosis rests almost entirely on the efficiency of renal control of this one component. The kidney, which has been described by MacCallum (1926) as the organ *par excellence* of evolution, maintains the chemical nature of extracellular fluid.

However, as emphasized by Gamble (1949), the kidney cannot entirely govern ionic concentration with a sufficient rapidity to meet the requirement for osmotic equality between extracellular and intracellular fluid, and thus there is a very important supplementary mechanism of osmotic adjustment behind the kidney, which has been demonstrated by the work of Darrow and Yannet (1935). The main feature of this mechanism lies in the fact that sodium remains in the extracellular phase, and its operation consists simply in the transfer of water across the boundary between extracellular and intracellular fluid in the direction which will produce osmotic equilibrium in the two fluids. Gamble (1949) illustrates this mechanism by showing that the addition of 15 grammes of sodium chloride to the extracellular fluid in the body necessitates a shift of approximately one litre of fluid to the extracellular phase. The opposite occurs on the withdrawal of 15 grammes of sodium chloride, and the kidney restores correct volume dimensions. Thus a failure of maintenance of the all-important plasma sodium level focuses attention upon the kidney tubules, and the question arises as to why this electrolyte depletion with hæmoconcentration and water shift occurs in pink disease.

Investigation into the functions of the adrenal cortex in this condition (Cheek, Hetzel and Hine, 1951, in preparation) reveals that if this disease is due primarily to dysfunction of this gland we must regard this dysfunction as being substantially related to the "salt and water" hormone. Such a concept is not new to pædiatrics. Jaudon (1946, 1948) detected an electrolyte disturbance in some infants

[1] Personal communication from Bivings.
[2] Personal communication.

in the early weeks of life, and he atttributed this finding to a temporary and fractional disturbance of the salt and water hormone of the adrenal gland. There is a syndrome in childhood called "*macrogenitosomia præcox*", which can be associated with hyperplasia of the adrenal gland and symptoms of adreno-cortical insufficiency. The children affected have a specific disturbance of their sodium and water balance. The first of these cases was reported by Butler, Ross and Talbot (1939), and since then many cases have appeared in the literature, which has been reviewed by the author elsewhere (Cheek, 1951). This condition is characterized by masculinization, which in the early days of life is more apparent in the female than in the male: girls are generally born as pseudohermaphrodites, whilst boys may not exhibit any secondary sexual abnormality for some months. Characteristic features are failure to maintain hydration, with anorexia, loss of weight and a craving for salt, and these children may progress to circulatory collapse, shock and death. Desoxycorticosterone acetate alone satisfactorily reverses the clinical picture. These infants have a raised 17-ketosteroid excretion, a lowering of the plasma sodium level, a rise in the plasma potassium level, and hæmoconcentration.

It has been thought that this condition is due to a disturbance of the sodium and water corticosteroid (Darrow, 1944; Barnett, 1949), and attention has been drawn to the relatively large doses (four milligrammes) of desoxycorticosterone acetate that are necessary to produce therapeutic results. The most recent investigations indirectly suggest that there is an excess glucocorticoid excretion, which causes an increased loss of body sodium (Mazursky and Sawan, 1950). Geppert *et alii* (1950) recently presented a case of fractional disturbance of adrenal function with biochemical, clinical and post-mortem evidence to support this view.

Thus it is quite possible that there is in pink disease a fractional disturbance of the corticosteroid regulating sodium and water metabolism. It is also possible that sodium depletion results from the effect of some obscure toxic agent acting on the kidney tubules, or from some other fractional disturbance of kidney tubular function. The progress of work at the moment has led me to favour this second viewpoint.

In states of salt depletion as a result of sweating, adrenalectomy or Addison's disease, salt alone has the effect of restoring the plasma sodium level to normal, but in pink disease salt alone does not restore normal plasma sodium levels (*vide* Table II). There is no reason to believe that the glucocorticoid excretion is excessively raised (Cheek, Hetzel and Hine, 1951). The fact that therapeutic benefit has been derived from attempts to restore correct osmotic relations is a reasonable indication that the electrolyte disturbance is responsible for many of the symptoms of this condition. However, from a study of some seventy cases it has become apparent that the photophobia, pinkness of the hands, loss in weight and muscle weakness of the infant sometimes seem to be little, if at all mitigated in the early stages of treatment. Treatment applied in a case of two or three months' duration may have spectacular results, as observed by Murray (1950) and as shown in some of these cases here reported. Some other important underlying factor in this disease probably remains to be elucidated.

It should be emphasized that it is the responsibility of the adrenal gland to maintain correct osmotic relationships and homœostasis (Sayers, 1950). If for any reason a severe electrolyte disturbance occurs, it places the adrenal cortex in a state of "stress" and renders the body unable to cope with any further added "stress", whether it be in the form of environmental heat, infection or some other non-specific agent (Selye, 1946). Such a state of affairs no doubt exists in pink disease. It is readily understandable why corticosteroids acting on the salt and water metabolism should have a beneficial effect; for they assist the adrenal gland and help to restore correct homœostasis.

There is as yet some other important factor to be determined in pink disease before the true nature of the condition and the rationale of treatment become clear. What this may be we can but speculate. It is possible that some toxic agent such as one of the little known photodynamic substances (*vide* Mathews, 1937) may be circulating in the blood-stream. During the course of our work it has been noted, from scores of samples of venous blood taken from children suffering from pink disease, that as soon as the erythrocytes begin to settle a peculiar orange-brown coloration of the plasma generally becomes noticeable. By subjecting samples of plasma to spectrographic absorption tests, curves have been found which show a typical graph for excess oxyhæmoglobin. One possible explanation of this finding is that it could be due to some toxin.

It is of interest to compare pink disease with those diseases in which a disturbance of porphyrin metabolism is known to occur—the porphyrins being perhaps the best known of the photodynamic substances concerned in human metabolism. Within recent years it has been found that salt depletion and low plasma sodium levels are a feature of the condition known as porphyria (Abrahams, Gavey and Maclagan, 1947; Linder, 1947; Davies, 1949). The last-mentioned author noted the occurrence of normal potassium levels, and enlargement of the adrenal gland was noticed *post mortem*. It is known that in this condition bizarre symptoms and signs become manifest. These include hypertension, tachycardia, sweating, abdominal pain, muscle weakness, photosensitivity, psychological change, cellular œdema, cachexia, oliguria, peripheral neuritis with paræsthesia, transient albuminuria and constipation (Nesbitt, 1944). It is also known that photodynamic substances can produce hæmorrhages and changes in the adrenal gland (Adler, 1920) and that a large group of non-specific factors, including anxiety, exhaustion, infections (Eldahl, 1938), drugs, metallic poisoning, cold *et cetera*, can precipitate acute porphyria in people constitutionally prone to this condition. In pellagra, in certain allergic conditions, and after the administration of certain drugs and metallic poisons, the porphyrin excretion is raised. Warthin (1926) was the first to compare pink disease with pellagra, and metallic poisoning has been repeatedly incriminated as the cause.

Preliminary investigation of the porphyrin excretion in pink disease, with the method of Fischer (1936) for coproporphyrin determination, and the method of Chandler, Harrison and Rimington (1939) for the uroporphyrin determination, has revealed in four cases a moderate rise in coproporphyrin excretion. No uroporphyrin could be detected. None of the children concerned was taking drugs or sedatives, and their ages ranged from two to four years. Twelve normal children of the same age group had a coproporphyrin excretion of 3 to 20 gamma per day. The subjects of pink disease had an excretion of from 30 to 50 gamma per day (repeated estimations).

The possible existence of photodynamic activity in this disease should receive closer attention and be evaluated. Australia has the highest incidence of rodent ulcer and possibly the highest incidence of pink disease. "Yet derangements in blood-pigment metabolism tend to develop during the 'General Adaptation Syndrome' as a result of stimulation of the reticulo-endothelial system" (Selye, 1950), and these preliminary findings possibly serve only to emphasize once again the importance of "stress" in pink disease.

Summary.

1. Eleven children (aged from two to seven years) suffering from the "later manifestations" of pink disease have been investigated. The preceding history in nine of the cases has extended over at least a year, and in some cases several years. In all cases the onset of symptoms was traceable to some "stress", such as measles or teething, as a starting point.

2. It is apparent that none of the bizarre symptoms of classical infantile pink disease are prominent in these children. Failure to eat and sleep well, failure to grow, psychological instability and lassitude are the main features; for this reason these children are indistinguishable from those with what has been generally regarded as the "nervous child" syndrome or athrepsia.

3. It is also shown that allergic manifestations are a concomitant feature in most of these cases, and that with treatment allergy seems to become quiescent. Eosinophilia is significant in most cases.

4. Restoration of health has been obtained in the presence of a mild electrolyte disturbance (plasma sodium level 300 milligrammes *per centum*) by treatment with salt alone. With a more severe disturbance five milligrammes of desoxycorticosterone acetate have been given until a satisfactory reversal of symptoms has taken place. Treatment of the patients has then been maintained with salt alone in all cases except one, in which a small implant of steroid by "Crystule" injection was given to maintain therapy. Treatment along these lines has to be continued for some months.

5. Salt alone does not restore normal osmotic relationships in most cases.

6. Estimation of the blood adrenaline content by biochemical methods in 18 cases of pink disease and in 24 normal children reveals no significant difference by this method.

7. Investigations as yet unpublished have revealed that if the adrenal gland is primarily involved in pink disease the factor concerned is the so-called "sodium and water hormone". Although this concept is supported by other related syndromes in childhood, the possibility is emphasized that the origin of the electrolyte disturbance in pink disease may lie outside the adrenal gland. Under these circumstances the gland is secondarily subjected to stress by virtue of its responsibility to maintain homœostasis.

8. It is suggested that further consideration should be given to the function of the kidney tubules and that the possible existence of obscure toxic or photodynamic agents should be further evaluated. Preliminary investigations reveal evidence suggestive of a disturbance in blood-pigment metabolism. This could be attributed to stress-producing agents.

Acknowledgements.

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PINK DISEASE: ITS RELATION TO ADRENAL FUNCTION AND THE VALUE OF SALT AND DESOXYCORTICOSTERONE IN TREATMENT.[1]

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PÆDIATRICIANS were stimulated recently by Cheek (1950) and by Cheek and Hicks (1950), who in two papers demonstrated that infants with pink disease had a low plasma sodium content and a high hæmatocrit value, and that treatment with salt and desoxycorticosterone successfully and rapidly restored them all to normal health. They also advanced an hypothesis that pink disease is "fundamentally an adaptation syndrome, the manifold manifestations of which are due to hypofunction of the suprarenal gland".

These claims were so striking that the following work was undertaken to test their validity: (i) The electrolyte pattern of 22 untreated patients suffering from pink disease and of 22 normal healthy infants was determined. (ii) Quantitative determinations of the 11 oxysteroids in twenty-four hour specimens of urine from eight of these patients and from seven normal infants of a similar age were carried out by Dr. J. Bornstein and Miss P. Trewhella, of the Baker Medical Research Institute, Melbourne, whose results are recorded in a letter in this issue (see page 385). (iii) A controlled experiment on ten patients was conducted, half of them being treated with salt and desoxycorticosterone, the other half receiving no special treatment.

The Electrolyte Pattern in Pink Disease and in Normal Infants.

The following methods were used to estimate the hæmoglobin and hæmatocrit values in the blood, and the sodium, potassium, carbon dioxide, chloride and protein contents of the serum of 22 untreated patients suffering from pink disease and 22 control patients. The control group comprised healthy children who were attending hospital for treatment of talipes or hernia, or for circumcision. The hæmoglobin value was determined with a Sahli-Hellige instrument (14·5 grammes = 100%). The hæmatocrit values were obtained by the use of a 1·0 millilitre Wintrobe tube and centrifuging for half an hour at approximately 3000 revolutions per minute.

The Serum Electrolyte Contents.

Sodium estimations were made by the gravimetric method of Butler and Tuthill, 0·2 millilitre of serum being used as described by Harrison (1947). The potassium content was determined by the method of Kramer and Tisdall (1921), 0·2 millilitre of serum being used. The chloride values were obtained by Whitehorn's method, as described by Harrison (1947). The protein content was estimated by the copper-sulphate drop method, described by Harrison (1947). Alkali reserve values were determined by the Van Slyke volumetric method, 0·25 millilitre of serum being used in a micro-apparatus. The column in which the gas was measured was of one millimetre bore and approximately seven inches long, the whole enclosing a volume of 0·5 millilitre, divided into hundredths of a millilitre. The method is described by Harrison (1947).

As serial determinations were carried out, the repeated bleeding of these infants made the use of smaller volumes of serum imperative. Sufficient blood can be obtained from a well-warmed foot if the heel is stabbed with a tenotome blade. One millilitre of blood was collected in one tube with a small drop of heparin for the determination of hæmoglobin and hæmatocrit values, and two millilitres were collected into another dry tube for electrolyte and protein determinations. All these estimations were made with smaller volumes of serum than those described in the original methods; the quantities of the other reagents were proportionately reduced. Before these methods were put into regular use, many duplicate deter-

[1] Read in part at a meeting of the Melbourne Pædiatric Society, October, 1950.

TABLE I.

Electrolyte Pattern of 22 Patients with Pink Disease and 22 Normal Patients.

Pink Disease.									Normal Controls.								
Patient.	Sex and Age in Months.	Electrolytes. (Milliequivalents per Litre.)					Hæmoglobin Value. (Grammes per 100 Millilitres.)	Hæmatocrit. (Volumes per 100 Millilitres.)	Patient.	Sex and Age in Months.	Electrolytes. (Milliequivalents per Litre.)					Hæmoglobin Value. Grammes per 100 Millilitres.)	Hæmatocrit. Volumes per 100 Millilitres.)
		Sodium.	Potassium.	Chloride.	Protein.	Carbon Dioxide.					Sodium.	Potassium.	Chloride.	Protein.	Carbon Dioxide.		
M.A.	F. 12	142	—	88	15	39	14·8	43·5	M.R.	M. 12	136	4	103	17	29	11·6	37·5
E.C.	F. 11	141	4	95	17	27	11·3	39·0	A.L.	F. 19	142	4	101	17	26	11·3	38·0
G.B.	M. 9	146	4	103	19	27	9·9	31·0	W.McL.	M. 6	141	4	109	14	22	11·0	33·0
J.F.	F. 15	139	—	108	15	29	14·5	42·0	M.T.	M. 7	137	6	111	16	24	11·3	38·0
B.D-F.	M. 15	137	4	94	17	31	13·5	43·0	R.S.	M. 6	136	4	111	13	22	12·5	41·0
G.G.	F. 11	122	4	97	15	—	12·2	43·0	P.W.	M. 12	140	4	104	15	22	12·8	40·0
N.H.	M. 14	145	5	92	16	44	12·3	43·0	A.C.	M. 10	143	5	102	16	32	11·0	36·0
G.H.	M. —	137	—	102	16	—	14·2	45·0	R.McD.	M. 14	136	5	100	15	22	11·6	39·0
S.H.	F. 9	149	5	100	16	32	15·6	48·5	A.W.	M. 24	137	5	104	15	22	13·0	43·0
R.L.	M. 8	124	5	86	17	29	11·9	40·0	R.W.	M. 6	136	5	104	15	28	13·3	41·0
P.L.	F. 15	143	5	108	16	27	11·7	40·0	D.L.	M. 23	141	4	104	16	24	12·1	38·0
R.M.	M. 9	141	3	100	15	24	12·1	41·5	P.C.	M. 19	142	4	104	15	22	11·9	33·0
S.McB.	M. 13	130	4	95	15	—	12·5	42·0	S.S.	M. 18	133	5	101	15	29	11·3	35·0
P.McD.	F. 12	135	4	99	16	29	10·4	37·5	P.P.	F. 19	137	4	101	18	29	12·1	38·5
B.McS.	F. 13	146	4	98	15	32	14·3	46·0	M.D.	F. 19	137	4	101	15	26	10·7	33·0
L.P.	M. 6	132	5	91	16	35	13·5	45·0	J.C.	M. 7	136	4	98	15	26	12·8	41·0
A.T.	M. 12	138	3	106	16	24	14·5	47·5	B.N.	M. 23	140	4	96	14	23	11·0	35·5
B.W.	M. 12	142	4	98	15	24	13·0	41·5	—.W.	M. 7	135	4	100	15	22	11·3	37·0
F.Y.	F. 12	139	4	95	17	34	13·9	46·0	J.C.	M. 6	138	5	101	15	27	11·3	34·0
G.C.	M. 8	146	4	112	15	26	12·8	40·5	N.S.	M. 8	144	5	103	16	25	11·9	38·5
P.G.	M. 11	143	3	102	18	27	12·5	42·5	C.B.	M. 12	136	5	99	15	31	12·8	40·0
D.J.	M. 9	140	5	98	16	28	10·1	38·0	J.O.	M. 8	137	4	96	15	23	12·2	40·0
Mean		139	4	98	16	26	13·0	42·3	Mean		138	4	102	15	25	11·9	37·6
Standard deviation		±6·9	±0·7	±6·5	±1	±6·6	±1·6	±4·1	Standard deviation		±3·1	±0·75	±4	±1	±3·3	±0·7	±2·9

TABLE II.
Clinical Phenomena Recorded by Observers.

General.	Skin.	Circulatory.	Motor.	Nutritional.
Demeanour. Irritability. Sleep. Interest in surroundings. Smiling. Play. Photophobia. Constipation. Temperature.	Sweating. Skin rash. Swelling and redness and coldness of hands, feet, face *et cetera*. Desquamation of skin, nails *et cetera*. Stomatitis.	Blood pressure. Pulse rate. State of peripheral circulation.	Muscle tone. Posture. Muscle power (judged by whether the patient can hold head up, sit, stand *et cetera*). Reflexes. Amount of spontaneous movement.	Appetite. Weight. State of subcutaneous tissue and muscles.

minations were made on samples of blood with the use of larger and smaller serum volumes, and very good agreement was obtained. In addition, samples of the serum of these patients were checked for sodium and potassium contents against the spectrophotometric method, at the Department of Physiology, University of Melbourne, and agreement was obtained within the limits of experimental error.

A number of these determinations were carried out immediately after the patient's admission to hospital and again at the end of a week's observation. No significant difference was noted in the two series of observations.

Statistical analysis of these figures shows that there is no significant difference in the serum sodium levels of the two groups, although two patients with pink disease have a very low serum sodium level. The hæmatocrit, hæmoglobin, protein and chloride values are significantly different on statistical analysis. The significance is 1%, or less than one chance in 100, for the hæmatocrit, and 5% or less than one chance in 20 for the hæmoglobin, protein and chloride values, that these differences are due to a chance effect.

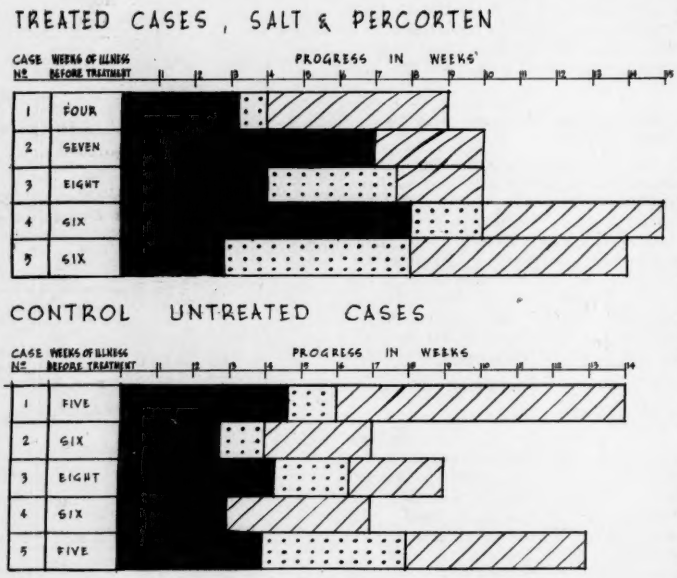

FIGURE I.

Graph showing comparison of results of treatment with salt and "Percorten" of five patients suffering from pink disease, with results in five control cases in which that treatment was not given; black section, no appreciable change; dotted section, slight improvement only; hatched section, steady and obvious improvement.

Experiment to Test the Value of Salt and Desoxycorticosterone in Treatment.

The design of the experiment was to select a group of patients with early, uncomplicated pink disease, put them in as stable a physical and emotional environment as possible, and treat half of them with salt and desoxycorticosterone and use half as a control group. A group of observers, who had no knowledge of which patients were being treated and which were not, then noted and recorded the course of the disease.

Four factors were carefully considered in this experiment, as it is exceptionally difficult to assess the results of treatment in a disease of unknown ætiology, of a subacute nature, of a variable clinical course, and with no quantitative yardstick to assess progress. Firstly, only patients in the early stages of the disease were treated, as the condition of many patients spontaneously improves during the third and fourth months. The results of any treatment instituted in the third and fourth months would be very difficult to assess. Secondly, any patients with a complicating lesion were excluded, as these complications frequently aggravate and prolong the illness. Treatment of such a complication often results in improvement. Infection, teething, inadequate nutrition or poor mothering is not infrequent, and children with any of these complicating factors were detected by the admission of patients to a small isolation ward for a preliminary period of observation under the care of a skilled nursing and medical staff. Thirdly, as progress can be assessed only by personal clinical observation, it is essential that the persons recording the progress of the illness have no knowledge of what treatment the patient is receiving. By this means personal bias is eliminated. Fourthly, a control group of patients is essential.

The routine adopted was that patients suffering from pink disease of less than six weeks' duration, who had received no treatment previously and were free of infection and any other complications, were admitted to a small ward which was used solely for these patients. These babies were cared for by a nursing staff, all of whom took a great personal pride in their welfare. To determine whether the baby was a suitable subject for the experiment, three independent physicians and the ward sister observed these babies for a period of one to two weeks. This enabled any complicating factor such as infection, teething, emotional upset or nutritional disorder to be detected. Also, the infant at the end of this period was well adjusted to his environment and nurses. If the observers considered that the patient was a suitable subject, he was included in the experimental group. The Clinical Research Registrar then gave treatment to half of these patients, the other half being used as a control group. The registrar himself added salt to the infants' feeding and himself gave injections of desoxycorticosterone to the treated group and of sterile water to the control group. He alone knew which patient was receiving treatment.

The ward sister and three physicians independently examined the patients at regular intervals, the ward sister every day, one of the physicians every second day, and the other two physicians two to three times per week, and recorded their clinical observations. The features in

Table II were noted and classed as "severe", "moderate", "mild" or "absent".

Of the 22 patients investigated, 12 were considered unsuitable for inclusion in the experimental group, as they either had been ill for longer than eight weeks, or had some complicating lesion. Ten patients were included in the experiment; all had an illness of similar severity, all had been ill for less than eight weeks at the time of commencement of treatment, and all were free from infection, teething troubles, emotional upsets or nutritional disorders. One of these patients had a low serum sodium content (124 milliequivalents per litre), while that of the remainder was within the range of normal. Five patients received treatment with salt and "Percorten" and five received no special treatment. The treatment consisted of the administration of five grammes of salt daily, given evenly divided in the infants' milk feedings, and this was continued until recovery occurred. Desoxycorticosterone in the form of "Percorten", in a dose of five milligrammes, was injected daily for two weeks, then every second day for one week and finally every third day for one week. All patients received nursing care and attention of the same high standard.

On completion of the experiment, each observer summarized his observations and recorded the period in weeks during which there was (*a*) no significant change, (*b*) slight but definite improvement in certain phenomena, (*c*) steady improvement till final cure. The assessment of all clinical observers approximated very closely. In the graph (Figure I) the average figures of all observers are recorded. The most reliable single criterion of improvement is a steady, continuous gain in weight.

It is interesting to record that one of the treated group had a low initial serum sodium content, 124 milliequivalents per litre, and this rose with salt and "Percorten" therapy to 152 milliequivalents, but there was no associated change in the clinical condition. One of the control group initially had a serum sodium content of 130 milliequivalents per litre; this fell to 120 and then rose to 141, and during these fluctuations there was no significant change in his clinical condition. There was no significant change in the serum sodium content of other members of the control or treated groups during the course of the disease.

Discussion.

A lowered serum sodium level, a raised potassium level and a low systolic and diastolic blood pressure are features which almost invariably occur at some stage in clinical cases of organic disease of the adrenal cortex, and in experimental lesions of the adrenal cortex (Cutler, Power and Wilder, 1938; Broch, 1945-1946). These features are not present in this series of patients, and it is therefore difficult to maintain that organic disease of the adrenal gland occurs in pink disease.

It is stated that pink disease is due to failure of adaptation of the adrenal gland to stress (Cheek and Hicks, 1950). At this stage it would not seem possible to prove or disprove this hypothesis. However, if pink disease was due to this cause, then one would expect a reduction in the 11 oxysteroid excretion in the urine of these patients. Bornstein and Trewhella have been unable to find any reduction in the 11 oxysteroid content of the urine of eight of these patients when compared with that of seven normal infants of similar age.

The hæmoglobin and hæmatocrit values are significantly raised and the chloride content is significantly low in this series of cases of pink disease. We are unable to offer a satisfactory explanation of these phenomena.

The clinical therapeutic trial shows that there is no significant difference in the course of the illness of those patients who were treated and those who were not. This clinical therapeutic trial was conducted on a small series of patients, for the reason that suitable and comparable patients were difficult to obtain. Twelve patients out of 22 suffering from pink disease had to be excluded because of a complicating factor such as infection or teething, or the fact that the mother was unable to cope with the feeding and general management. Some also had been ill for longer than six weeks when first examined. As far as has been possible we have used comparable patients, have eliminated variables, and have submitted the experiment group to an unbiased assessment. Any difference in the results between the treated and untreated patients is not significant.

In a number of the cases during the preliminary period of observation there was a considerable rapid relief of symptoms, and this was due, we believe, to better nursing and mothering than the infant had been given at home. If these patients had received special treatment as soon as they were admitted to hospital, it would have been impossible to say that this improvement was not the result of this special treatment.

Summary.

1. There was no constant or significant disturbance of the serum sodium content of 22 patients with pink disease as compared with 22 normal children of the same age as determined by chemical analysis, although two patients had a low serum sodium level.

2. The hæmatocrit, hæmoglobin and protein values are raised and the chloride content is lowered significantly in pink disease as compared to the findings in normal children, and the nature of these changes is not understood.

3. There is no evidence of hypofunction of the adrenal gland as determined by any alteration of blood sodium and potassium levels, or lowering of excretion of the 11 oxysteroids in the urine.

4. A controlled clinical experiment on 10 selected patients failed to detect any really significant difference in the recovery rate of the five treated with salt and desoxycorticosterone as compared with those who did not receive this treatment.

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Our thanks go to Miss I. G. Nicholls, the ward sister, and her nurses, to whom the highest credit is due for first-class nursing and mothering of these patients. We wish to thank Dr. Robert Southby and Dr. V. L. Collins, who acted as two of the medical observers, and also the honorary medical staff of the Children's Hospital, Melbourne, who so generously referred patients to us. We also thank Dr. J. Bornstein and Miss P. Trewhella, of the Baker Medical Research Institute, for kindly undertaking the oxysteroid estimations in the urine of these patients.

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A NOTE ON A PLACENTA-PERMEATING ANTI-M AGGLUTININ.

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AGGLUTININS active against the M and N factors are still rare enough to warrant recording. We have seen only sixteen references to examples of anti-M agglutinins found in human serum. Those described by Wolff and Jonsson (1933), by Friedenreich (1937), by Moureau and Lambert (1939), by Davidson and Schirmer (1941), by Dahr (1941), by Hamilton Paterson, Race and Taylor (1942), by McFarlane (1945), by Van der Spek and de Kromme (1948), by Moullec (1948), and by Bowley and Dunsford

(1949) have been regarded as naturally occurring, and the remainder, described by Wiener and Forer (1941), by Wiener (1942), by Broman (1944), by Wiener, Gordon and Mazzarino (1948), by Malone and Cowen (1950) and by Wiener (1950) as due to immunization.

We ourselves have encountered four cases in which anti-M agglutinins were present, all of which we regarded as naturally occurring.

One of these four agglutinins is the subject of this note. It was found during the routine ante-natal investigation of a woman attending the Queen Victoria Hospital. Her first pregnancy in 1945 resulted in a living female child, her second in 1948 in a miscarriage at three months, and her third in 1949, the pregnancy under discussion, resulted in a living full-term male child, with no abnormal features likely to be due to iso-sensitization.

The serological investigations revealed that the mother's blood belonged to group A (subgroup A_1), N, Rh_2 (cDE/cde); at the third and ninth months of her third pregnancy, and at delivery, her serum was found to have an anti-B titre of 64 at room temperature, and also an abnormal agglutinin. Tests at room temperature, at 4° C. and at 37° C. with cells from a selected panel of twenty-five persons showed that this agglutinin was anti-M.

The child's blood group was O, N, Rh_1 (CDe/cde). The Coombs test on the cord blood gave a negative result; no anti-A or anti-B agglutinins were demonstrable, but the anti-M agglutinin was present in the same titre as in the mother's serum. In neither maternal nor infantile sera did the agglutinin react with cells containing the M variant described by us in a previous paper (Jakobowicz, Bryce and Simmons, 1949).

In a sample of the child's blood taken on the sixth day, the anti-M titre was the same as that in the cord blood, but five and a half months later it had almost disappeared. At the latter time, it is interesting to note, an anti-A agglutinin was just demonstrable.

The details concerning the anti-M agglutinin in the maternal and infantile blood are shown in Table I.

Discussion.

At the time of identification of the anti-M agglutinin in the cord blood, we considered the following two possibilities.

1. This agglutinin, present in both maternal and cord blood, may have been of hereditary origin. This possibility seemed at first the more likely, as our previous experience had been in accord with the concept of Wiener (1948) that antibodies of the agglutinating type do not pass the placenta, since in the occasional cases in which agglutinins such as anti-P, anti-Le^a, Le^b, or anti-O have been identified by us in the serum of pregnant women, there has been no instance of passage of these agglutinins from mother to fœtus. In this case also, the normal maternal anti-B agglutinin was not found in the cord blood.

2. On the other hand, the equality of titre of the anti-M agglutinin in the maternal and cord blood suggested passive transfer, and this possibility seems to be supported by the later drop in its titre in the child's blood.

The third child, being of type N, could not have sensitized his mother. We have no data concerning the M and N factors in the elder child, or in the aborted fœtus, but even if they were such as to provide the possibility of sensitization of the mother, it seems unlikely that the titre of a resulting agglutinin would have remained constant throughout the later twelve months' period during which she was under our observation. The agglutinin was more active at 4° C. than at room temperature, and was inactive at 37° C. These facts support the opinion that it is a naturally occurring rather than an immune agglutinin.

Our assumption that this anti-M agglutinin passed through the placenta appears to indicate that it is of smaller size than the majority of other blood factor antibodies of the agglutinating or "saline" type.

Summary.

1. An anti-M agglutinin is described, which was found in the blood of both a mother and her new-born child.

2. The observations suggest that this agglutinin was a naturally occurring one which was passively transferred through the placenta from the mother to the child.

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Table I.

Titre of Anti-M Agglutinin in Serum of Mother and Child.

Date.	Temperature.	Mother's Serum: Cells Tested.[1]				Child's Serum: Cells Tested.[1]			
		M.	M_2.	MN.	N.	M.	M_2.	MN.	N.
11.8.49	4° C.	120	0	16	0				
	Room temperature	16	0	2	0				
	37° C.	0	0	0	0				
15.12.49	4° C.	250	0	16	0				
	Room temperature	8	0	2	0				
	37° C.	0	0	0	0				
18.2.50 (Delivery)	4° C.	120	0	16	0	120	0	16	0
	Room temperature	16	0	2	0	8	0	4	0
	37° C.	0	0	0	0	0	0	0	0
24.2.50	4° C.	120		16		120	0	16	0
	Room temperature	16		2		8		4	
	37° C.	0		0		0		0	
3.8.50	4° C.	120		16		2			
	Room temperature	16		2		Trace			
	37° C.	0		0		0			

[1] The figures in the third and fourth columns are the reciprocals of the first dilutions in which agglutination occurred.

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CEREBRAL TUMOUR: EARLY SYMPTOMS AND METHODS OF INVESTIGATION.

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THE frequency of expanding lesions of the brain is nowadays well known. Yet the average practitioner may see few, compared with the common ailments of the heart, lungs and abdominal organs. None the less the onus of early suspicion, or recognition, falls on him, and his task is made all the more difficult by the many and varied habits of these lesions. Therefore it may be helpful to give wider circulation to current experience in a unit handling these cases.

There is no simple list of the early symptoms of brain tumour, such as may be given for pulmonary or cardiac or gastro-intestinal diseases. We are always being surprised (and often confounded) by the varied and subtle ways in which cerebral tumours disclose themselves. But this is not to be wondered at when one considers the countless aspects of body function and human behaviour which are linked with the brain.

The cases submitted here were chosen originally for a clinical meeting at the Alfred Hospital as examples of some of the ways tumours present. They are selected from over forty cases of proven intracranial neoplasm in patients who passed through the neurological and neurosurgical wards of the hospital during the past year, and two cases of non-neoplastic expanding lesion have been added. Having been picked for this primary reason, they are in no way indicative of the relative frequency of the pathological types, or location of tumours within the skull. Nor do I claim to add anything new of scientific value to the existing knowledge of the subject.

Principles of Diagnosis.

The principles of neurological diagnosis are the same as for any branch of medicine.

The complexity of the central nervous system and consequently its variety of symptoms of disorder does, however, impose the need for vigilance in observing these principles, in what amounts to a strict discipline of logic. But the ordered nature of its anatomy (and so physiology) lends itself to this.

Firstly one must decide: Is there a lesion at all? This is above all a matter of pure clinical judgement. In fact the answer to this question depends on the recognition of disturbance of function: the elicitation and evaluation of history and physical signs. It is wrong to start a patient needlessly on the long and tiresome road of complete neurological investigation, just as it is to fail to do so when the need exists.

The second question is: Where is the lesion? It may be thought naïve to write that there is sometimes difficulty in deciding whether a disorder of, let us say, pyramidal function is caused by a lesion in the spinal cord or brain. When the evidence conclusively incriminates the brain it is often hard to say which side, and very frequently a problem to be sure which lobe. Careful examination and clues from the history help a lot in answering this second question; but special investigations are often necessary to do so, and in fact always necessary for an exact diagnosis, where tumour is concerned.

The final question is: What is the lesion? Whether or not it is an expanding lesion must first be settled, and if it is expanding, its nature must be determined. The history helps most in the first part of this question, and often a great deal in answering the second part. Full investigation and even craniotomy are often necessary to settle the matter definitely.

The Methods of Investigation.

It is intended to make only brief comments with references to some points of current experience which may be helpful.

Presenting Symptoms and History.

Headache and epilepsy are two dominant symptoms: but there is often no epilepsy and even headache may be absent.

Although there are features of the headache of raised intracranial pressure which help in differentiating it from other headaches, generalizations on this subject are unreliable. Furthermore, the headache which is referred to at this point may be present long before the pressure rises. Experience is that it has no invariably characteristic features. Persistent or recurrent headache should raise the suspicion of intracranial disease unless the headache has positive features or associations which indicate some other cause. For example, a diagnosis of migraine is justified when it occurs periodically in an otherwise healthy person with a family history, or with sensory or visual aura of characteristic pattern. Nevertheless one has had experience of more than one case accepted as migraine for many years before a tumour was proved to be present. One case appears below (Case III). It is of course hard to say whether the two are related or coincidental. In angioma of the brain the headache may mimic migraine. It did not do so in the case quoted below, but another case is recalled in which it did.

Epilepsy must be considered as a symptom and not as a diagnosis. Epilepsy of late onset, that is, after the age of twenty-one years, is a positive indication for a full-scale investigation, unless there is a readily apparent cause, as in eclampsia or uræmia. I believe that there is no qualification to this statement. The cause is very frequently organic, but not necessarily tumour.

Completely normal findings do not mean that there is no tumour; they mean only that a tumour cannot be demonstrated with the methods available. The situation should be reviewed completely at intervals of not more than a year. It is not rare for evidence of a tumour to be disclosed at one of these "reinvestigations". Uncomfortable as these investigations may be for the patient, it is worth while if a benign meningioma can be removed—memory of such a patient prompts this statement.

For epilepsy beginning at any earlier age the label of "idiopathic" should be applied only after the most careful scrutiny of all the facts (Case II). Tumour is present in some cases; congenital defect, birth trauma or other organic lesions which occur during infancy may be demonstrated in many other cases. The residual signs of a hemiparesis which occurred in infancy may be minimal when

the child is examined some years later. Air study is often helpful in disclosing an organic cause.

It is not suggested that all juvenile epileptics should have a full-scale investigation, but at least the results of careful neurological examination and X-ray examination of the skull should be normal before the diagnosis of idiopathic epilepsy is accepted.

"Focal" Symptoms.

"Focal" symptoms may be the first, and their great variety is merely a reflection of the many facets of function and behaviour which are influenced by the brain. Predominant in this group is, of course, focal epilepsy. This may be of the true Jacksonian motor type and consist of focal sensory attacks, or may be purely psychic, such as in the hallucinatory aura of smell, vision or hearing. Even motor attacks may not be recognized for a time, but the rarer forms of sensory attack may elude us if we are not aware of their guises. Those with origin in the temporal, parietal or occipital lobes may cover such a range of psychic experiences that the possibility of their organic origin may be reasonably suspected only by their episodic occurrence or the progression of an attack to a major convulsion. In the differentiation of sensory epilepsy from the sensory aura of migraine the time of spread and duration of the sensations are important criteria. In epilepsy both are usually momentary; in migraine the sensations may take several minutes to spread from the point of origin, and the whole aura may last for half an hour or more.

It is important to add that Jacksonian motor attacks may last much longer, even hours, without any alteration of consciousness, and perhaps be confined to a corner of the mouth or to one hand or foot.

Another clue in the history sometimes found in cases of tumour is that the nature of the attacks changes over the course of time or the patient may be aware that his attacks may variously take two or even three different forms.

Other focal symptoms may range from stiffness of the fingers or toes (minor defects of voluntary movement are referred to by patients as anything from numbness to rheumatism) to disturbance of bladder function, or even metabolic disturbances such as gain in weight, or subtle changes in personality or intellect.

As such disturbances of function may have so many other causes, the difficulties of evaluating and relating them to disturbed cerebral function cannot be overrated. It may not be until they are associated with some other more specific complaint, such as headache or epilepsy, focal or general, or accompanied by some positive neurological signs that their true significance can be appreciated.

If there is any generalization worth stating in such a brief commentary as this, it may be that a tumour usually produces a slow but inexorable march of events, sometimes spread over years—occasionally even more than twenty years. Yet it may announce its presence with dramatic suddenness, as in Case III.

The necessity for patience in taking a detailed and accurate history in a suspected case need hardly be stressed. Checking the patient's statements with a close relative is sometimes illuminating and often helpful. For the proper assessment of altered consciousness, episodic behaviour or personality changes it is essential. Furthermore, the interviewing must be done by the doctor and not by a sister, an almoner or a medical social worker. The importance of delving back to the very first symptom for its localizing value has long been taught.

Headache, vomiting (and papillœdema) signify that the functional compensation for the space occupied by a tumour has broken down. These features are late—often too late—in the life history of the tumour. The whole purpose of our endeavour is to diagnose space-occupying lesions before this occurs. Raised intracranial pressure greatly increases the hazards of investigation and surgery. When a tumour is benign and operable, the advantages of doing something before these additional risks are imposed are obvious. Frequently the pressure rises rapidly, long after the appearance of early symptoms.

Examination.

It is important to make some assessment of the patient's mental state. If it can be firmly established that there has been a change in personality or intellectual capacity, this may help in deciding that the cause of some other accompanying disturbance of peripheral function is also located in the brain. Thus its "localizing" value is important.

It is remarkable how changes of personality or intellect may for a long time be unrecognized by the patient or his relatives. The insidious and ingravescent nature of these changes no doubt accounts for this. If noticed, they are often attributed by relatives to some exogenous cause, such as worry or overwork, and are accepted as such.

On the doctor's side care is necessary to distinguish between organic mental deterioration on the one hand and neurosis or psychosis on the other. One has seen indifference and apathy accepted as depression, irritability as neurosis, and violent and hilarious behaviour as mania, when the cause in each case has been tumour.

A patient formerly intellectually above average may preserve a façade in his deteriorated state. One is sometimes surprised when a patient has been talking rationally, answering questions quite aptly, and perhaps has even given a reasonable history, then to find by a few simple questions that he does not know the day of the week, the date, or even the year, or is quite uncertain where he is or what he had for breakfast a few hours previously. Such subjects of disorientation or recent memory defect may give most amusing answers to such questions as "Who is the King?" or "Who is the Prime Minister?", slipping back even a generation or more in their replies.

In less gross changes of intellect the application of some simple psychometric tests may be necessary to form an opinion. These may be applied by a trained neurologist or, if there is still doubt, by a psychologist or psychiatrist. It is the "falling back" from a previous intellectual level which is important. Sometimes only one aspect of intellect is specifically affected. Care is necessary to differentiate apparent deterioration of intellect associated with a neurosis.

Aphasia may also mislead. When this is predominantly "sensory" in type, the patient is thereby unable to understand his own speech. He may thus be most voluble and give the impression of being "all at sea". His otherwise reasonable behaviour or apparent distress at being out of contact with his fellow man may give a lead to the true nature of his trouble. Special tests for dysphasia will usually decide the issue. Minor degrees of speech defect need careful analysis to establish their true nature and significance.

The physical examination must be full and careful. It is the evaluation of signs elicited which usually counts so much, and this is a matter of skill and experience, in which no one ever reaches the stage of infallibility. We are perhaps learning to recognize earlier the signs of disorder of willed movement. The writings of Walshe (1947) state the present position admirably.

The difficulties of deciding when early papillœdema is present will be, I think, recognized by all, including ophthalmologists, whose help should be sought when there is doubt. The special difficulties of hypermetropic disks and disks with surface glial tissue have been known to beset even the most experienced. It is well to know that such "catches" can occur; but they should not deter us, because the more severe grades of swollen disks with hæmorrhages can be seen by all.

The special importance of examination of visual fields needs no stressing. The visual pathways traversing the whole length of the brain, fore and aft, are thus more liable than any other system to interruption by destructive lesions. Simple confrontation methods, which any doctor can use, usually detect all but the slightest defects and are thus invaluable. The use of a small white-headed pin, pushed into a stick, is very helpful in doubtful cases. Ultimately the fields should always be charted accurately with a perimeter and Bjerrum screen.

It need hardly be said that a proper general examination is a corollary to a neurological examination, and to see the patient walk is part of it.

Finally it must be stated most emphatically that "no physical signs" does not mean no tumour (Case XII).

Special Investigations.

If a critical comment is allowable, a statement relative to lumbar puncture is thought to be most justifiable. When tumour is suspected this procedure seems to leap to mind more readily than anything else. This arises no doubt from thoughts of raised pressure. Very frequently the pressure is "guessed" from the "rate of drops", which is absolutely valueless if no manometer has been used. If the pressure is raised by measurement, it is much better for the puncture not to have been done; certainly not until several other things have been done. If the pressure is normal, even with a normal rise and fall on jugular compression, the presence of tumour is by no means excluded. (The term "Queckenstedt positive" may have different meanings in different minds, and is therefore better replaced by a factual statement of observations made.)

The results of chemical examination of the fluid may also be quite normal in the presence of tumour (Cases V, IX and XII).

When the pressure is raised the danger is the escape of fluid with lowering of pressure leading to "coning" of the hind brain into the *foramen magnum*. With both supratentorial and infratentorial tumours this can produce sudden death and often leads to deterioration of the patient's condition sufficiently to curtail further desirable investigations, and to make urgent surgery necessary under conditions less favourable than they might have been.

After physical examination (including the optic fundi and fields), whether there are positive findings or not, if the history has raised suspicious of an intracranial expanding lesion, the investigations of first importance are plain X-ray examinations of the skull and a blood Wassermann test. A full series of standard views should always be taken, and it is a sound rule always to take skiagrams of the chest at the same time. The skull plates should be of the highest quality of technical perfection available, and, ideally, should be interpreted by a radiologist trained in neuroradiology and freely available for consultation with the physician. Minutiæ, such as tiny specks of calcification, may be of decisive importance. Again negative findings are by no means exclusive of tumour.

It has been my experience, here and abroad, that routine skull X-ray examinations and examination of the blood Wassermann reaction in all cases of epilepsy (at any age) and all cases of recurrent or persistent headache without apparent cause, every now and then produce an unexpected finding of telling importance.

Electroencephalography is part of a full-scale investigation. Its usefulness, technically adequate records being assumed, is proportional to the experience of the interpreter. Cobb (1944) has demonstrated correct localization in approximately 50% of cases of supratentorial tumour. In practice it is normally used only as supporting evidence for the presence of an organic lesion and its localization; but it can give useful information of the type of lesion, especially with abscess and subdural hæmatoma. Rarely it may disclose a lesion not revealed by other methods. Inexperience, especially of interpretation, necessarily restricts its usefulness in our hands at present.

After completion of the investigations so far mentioned and other subsidiary procedures indicated by the special features of a given case, lumbar puncture is considered. If no evidence of raised pressure has been found in the fundi or X-ray films, lumbar puncture is performed, the pressure and response to jugular compression are carefully noted, and the fluid is examined for cells, protein, Wassermann reaction and colloidal gold curve, and frequently culture is required for torula and other organisms. If the pressure is known to be raised (or found to be raised), puncture is usually performed, but with special care to avoid leakage of fluid, and the pressure is measured with a fine-bore manometer. Only sufficient fluid for really essential examinations is collected, that in the manometer being included.

It is realized that there are other views on this subject. Some surgeons prefer to receive their patients for operation without any prior disturbance of intracranial hydrodynamics at all, and so specifically request that in suspected tumour cases patients known to have raised pressure be referred without lumbar puncture. Fluid obtained at ventriculography is then submitted for Wassermann test and other studies.

The final steps in investigation short of craniotomy are air study and carotid angiography (by arterial puncture through the skin). As a generalization these two methods are complementary: air for localization and angiography for pathology. In more and more cases we are preferring to carry out the angiography first, for two reasons: it is less troublesome to the patient than lumbar air encephalography, and with some lesions, especially with meningioma and subdural hæmatoma, both the exact site and the nature of the tumour are disclosed, so that air studies become unnecessary.

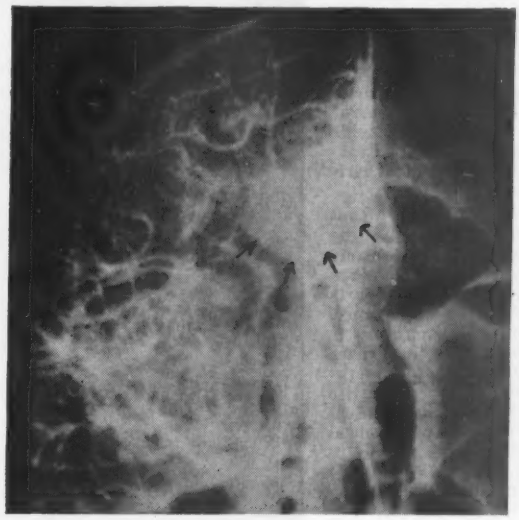

FIGURE I.

If air studies are to be made, the guiding principle is to use the lumbar route if there is no increase of intracranial pressure; otherwise ask the surgeon to make a ventriculographic examination. The advantages of the lumbar route are that the hair need not be shaved (which is important if the findings do not indicate subsequent operation) and that in addition to the showing of the ventricular system some air passes over the convexity of the brain. This gives specially valuable information in degenerative cortical states (including cerebral vascular disease), which sometimes cannot be differentiated from tumour with certainty until this stage of the investigation.

Even normal air studies with pictures in all the standard positions do not exclude neoplasm. One reason, the presence of an early tumour, has been mentioned already. Another is that with tumour in the middle fossa there may be no deformity of the ventricular system in standard views. Thus, in the presence of special indications, additional posturing is necessary to fill the temporal horns and take appropriate pictures of these (Lindgren, 1948).

Occasionally all the investigations may be inconclusive and craniotomy may be necessary to determine whether a lesion is present or not. This happened in one case during the past year (not included amongst the cases quoted), and biopsy disclosed an astrocytoma. Much more often the nature of the tumour remains unknown until craniotomy and biopsy are carried out. There is sometimes a temptation to spare the patient this final step, in the belief that

he is harbouring an inoperable glioma. The reason for resisting this is that a meningioma or even a subdural hæmatoma is sometimes found when least expected.

Conclusion.

No single method of investigation answers the three fundamental questions: Is there a lesion? Where is it? What is it?

There are no short cuts, therefore the rational application of the methods of clinical study, in their ordered sequence, is essential for precise diagnosis—the prerequisite to effective surgery.

In every phase of the study of these cases the aim must be the highest perfection of skill. A trivial sign or radiological finding, if unequivocal, may be of decisive importance and alter the whole course of management. It will be apparent from what has been said that a wide range of specialist knowledge may have to be called to aid in a thorough study of any one case and that this needs teamwork in timing and coordination, and, finally, careful assessment. This still demands sound clinical acumen, for which no machine or technical skill can substitute. An error of judgement or logic may annul all advantages gained therefrom.

Despite all that may be said, the recognition of early symptoms and signs by the practitioner is of first importance. For this nothing is ever likely to surpass the value of a knowledge of the life history and clinical behaviour of cerebral tumours.

Clinical Histories.

These clinical histories are presented in a tabulated form, so that the main features may be more quickly selected. Two cases (VII and VIII) are not cases of neoplasia, but have been added because, in common with cases of that type, they illustrate the behaviour of expanding lesions, but have special features relative to the conditions they represent; and they show the diagnostic value of angiography in these cases.

CASE I.—A woman (K.M.), aged thirty-five years, was admitted to the Alfred Hospital under the care of Dr. Leonard Cox on November 3, 1949.

First Symptoms.—Her first symptom had been a queer feeling "as if the right foot and leg were not there for about three or four minutes" sixteen weeks before admission.

History.—Further similar attacks had followed, involving the right leg and right shoulder and arm, followed by jerking of these limbs for about five minutes (Jacksonian attacks). There was no loss of consciousness. Attacks were followed by aching in the limbs and headaches. The patient admitted, on questioning, to headaches for seven years, but they had been much worse for the two weeks preceding admission to hospital, and she had been vomiting in the mornings. On being questioned, her husband recalled occasional twitching of the patient's right arm and leg in bed for six years—not noticed by the patient.

Signs.—There was no papilloedema or field defect. There was very mild right hemiparesis following attacks, with complete recovery at times (Todd's paralysis). She was a nervous, anxious person without mental deterioration.

Investigations.—The X-ray appearance of the skull was normal. Lumbar puncture pressure was 120 millimetres of fluid. The fluid contained 70 milligrammes *per centum* of protein, but was otherwise normal. Air encephalography showed displacement of the left lateral ventricle. Percutaneous angiography showed vessel displacement and "blush" (persistent in phlebogram) in the left pre-Rolandic area (Figure I).

Diagnosis.—The diagnosis was meningioma.

Operation.—A meningioma was removed.

Result.—The patient is now leading a normal life and is symptomless.

CASE II.—A woman (C.B.), aged twenty-two years, was admitted to the Alfred Hospital on September 29, 1949, under the care of Dr. Leonard Cox.

Presentation.—She had had "idiopathic" epilepsy since the age of seven years.

History.—At the age of thirteen years she had *status epilepticus*. The last attack of epilepsy was during pregnancy, fifteen months before admission to hospital. She had had headaches for six months, which had been relieved by "powders". Vision had been dull and misty for two weeks.

FIGURE II.

Examination. — The findings were bilateral papilloedema with pale disks, an incomplete homonymous field defect, and very mild and transient right pyramidal signs.

Investigations. — X-ray examination of the skull showed punctate calcification of the left posterior parietal region; the posterior clinoids were thin; there was no pineal calcification. The cerebro-spinal fluid pressure was 350 millimetres of fluid. The fluid contained 60 milligrammes *per centum* of protein, but was otherwise normal. Percutaneous cerebral angiography showed a collection of abnormal vessels in the left posterior parietal area. The presence of tumour was presumed, but there was no indication of the type.

Operation.—Ventriculography was performed—a cyst was needled in the left occipital region and filled with air. An invasive tumour was removed from this site. Examination of a section showed a highly cellular glioma with no observed mitotic figures and not highly vascular. Deep X-ray therapy was given.

Present State.—Vision is worse. There is secondary optic atrophy with flat disks. Other symptoms and signs were relieved for some months, during which she had deep X-ray therapy; but the patient is deteriorating rapidly again now.

CASE III.—A man (A.W.), aged forty-five years, was admitted to the Alfred Hospital on August 30, 1949, under the care of Dr. Leonard Cox.

First Symptom.—His first symptom was "headaches all his life—like the family". (The informant was a brother.)

History.—Six weeks previously he had had a severe attack of vomiting, which was self-diagnosed as "ptomaine poisoning". Six days before admission to hospital he had right facial "neuralgia" and visited a dentist, who found no fault with his teeth. Five days before he had pain behind the eyes, for which he used eye drops. Three days before he "became delirious", and had become "more stupid and sleepy since". The brother, when pressed, said that the

patient was "a reserved, but interested, man, but for two months has been disinterested, surly and irritable".

Examination.—The patient was stuporose. He had slight papilloedema, present bilaterally. The right pupil was dilated, the left constricted, and there was no light reflex. There was divergent strabismus. There were increased deep reflexes in the left arm and leg, and the left plantar response was extensor in type.

Investigations.—X-ray appearances of the skull and chest were normal. Lumbar puncture pressure was 50 millimetres of fluid with no rise and fall on jugular compression. The cerebro-spinal fluid contained 24 polymorphonuclear leucocytes and four lymphocytes per cubic millimetre and 80 milligrammes *per centum* of protein.

Operation.—Ventriculography showed a pronounced "shift to the left". Right temporal craniotomy showed a soft cellular invasive tumour in the lower medial portion of the right temporal lobe, well forward.

Result.—The patient died. At autopsy an astrocytoma was found.

CASE IV.—A man (W.P.), aged forty-nine years, was admitted to the Alfred Hospital on September 5, 1949, under the care of Dr. L. B. Cox.

First Symptom.—He complained of loss of libido for one year.

History.—He felt perfectly well, and his waning sexual activity was his only personal complaint. On questioning he said that he had changed jobs five or six times in the last twelve months—his "mental processes, particularly calculations, don't seem to keep up" with his hands. His occupation was a fitter. He had had frontal headaches for twenty years. On questioning his wife revealed that he was gaining weight rapidly. His personality had changed in that he had become a little coarse and lewd in conversation in the family circle. He was a little careless about bathing, and had wet the bed twice at night.

Examination.—He appeared a jovial, easy-going fellow, a little unrestrained, and with no insight into the facts given by his wife. He was well orientated in time and space, and his memory of recent and remote events was defective in minutiæ only. There was complete anosmia and loss of flavours in taste. Examination of the visual fields showed loss of the upper half of the field of the left eye, and right upper quadrantic loss in the right eye. The disks were flat. There were trivial left pyramidal defects, and a left extensor plantar response.

Investigations.—X-ray examination of the skull showed erosion of the posterior clinoids. The cerebro-spinal fluid contained five lymphocytes per cubic millimetre and 200 milligrammes *per centum* of protein. Encephalography showed distortion and displacement of both frontal lobes (Figure II). Right and left carotid percutaneous angiography showed both anterior cerebral groups to be deformed with convexity anteriorly (Figure III). There was "blush" in the deforming mass.

Operation.—A large olfactory groove meningioma was excised.

Result.—The fields of vision improved. He still has a jocular manner and is "a great talker". He says he is very well.

CASE V.—A woman (M.G.), aged fifty-six years, was admitted to the Alfred Hospital on March 5, 1949, under the care of Dr. L. B. Cox.

First Symptom.—The left ankle had became weak twenty months before admission to hospital.

History.—For twelve months she had had attacks—"a creeping sensation up the left leg and trunk to the left ear where it became pins and needles" (Jacksonian). These attacks became more frequent until finally she had several a day. Headaches had begun twelve months before admission to hospital, but were less frequent at the time of admission. Her left leg had become weaker, and the left hand also.

Examination.—There was bilateral papilloedema, with mild pyramidal weakness of the left leg, and to a less extent of the arm. The sense of passive movement and two-point discrimination were defective in the left foot.

Investigations.—X-ray examination of the skull showed a small area of rarefaction and some hyperostosis in the right parietal parasagittal region. The cerebro-spinal fluid pressure was 320 millimetres of fluid, and the fluid contained seven lymphocytes per cubic millimetre and 30 milligrammes *per centum* of protein. Ventriculography showed a "shift to the left" with depression of the roof of the right lateral ventricle.

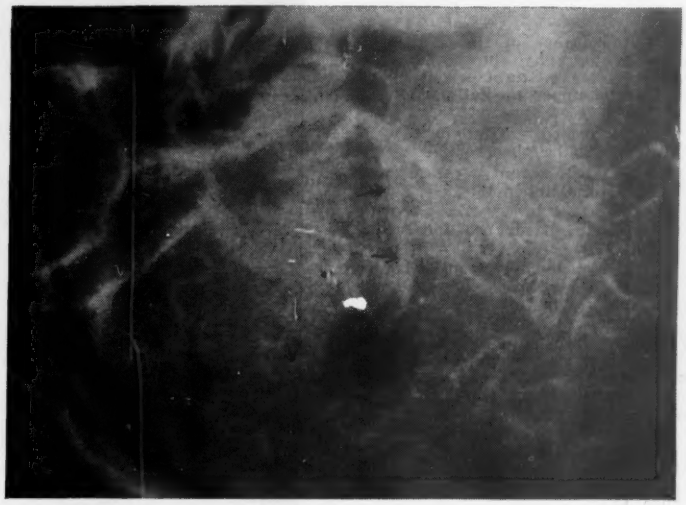

FIGURE III.

Operation.—A parietal parasagittal meningioma was removed. Examination of a section showed meningioma.

Result.—The papilloedema subsided. There was a residual left hemiparesis. The patient, by letter, states that she is improving slowly.

CASE VI.—A woman (C.R.), aged fifty-two years, was admitted to the Alfred Hospital on October 21, 1949, under the care of Dr. L. B. Cox. This patient had two tumours.

First Admission to Hospital.—Nine years previously a left cerebellar hæmangioma and cyst had been removed by Dr. H. C. Trumble. The original symptoms had been dull occipital pain and giddiness for ten weeks. Papilloedema was present on admission to hospital. After the operation she remained well until the year of her recent admission.

Second Admission.—The presenting features on her second admission to hospital were "loss of interest and depression".

History.—She realized that her "thinking had become slow". She was muddled and confused about simple tasks. She could not read, she said, "because I cannot remember the names of the letters of words", and she also complained that "I can see things clearly, but some objects do not seem to make sense, and some scenes I look at do not mean anything". (This is interpreted as defective visual perception or visual agnosia.)

Examination.—The right eye was blind (cataract). The left eye had a right half-field defect. The visual acuity of her left eye was difficult to assess on account of her "word blindness", but was thought to be at least 6/12. The fundus was normal, and there were no other signs in the central nervous system.

Investigations.—X-ray examination of the skull showed the pineal gland to be a quarter of an inch to the right of the mid-line. The cerebro-spinal fluid contained four lymphocytes per cubic millimetre and 80 milligrammes *per centum* of protein. Encephalography showed a shift to the right and deformity of the posterior portion of the left lateral ventricle.

Operation.—A left occipital tumour was partially removed, but the patient died.

Autopsy.—There was no recurrence of the old cerebellar tumour found at autopsy. Examination of a section of the recent tumour bed showed a highly malignant anaplastic tumour. There was a small cyst 1·3 centimetres in diameter in the opposite cerebellar hemisphere.

CASE VII.—A woman (E.D.), aged thirty-eight years, was admitted to the Alfred Hospital on October 17, 1949, under the care of Dr. L. B. Cox.

First Symptom.—She had had "fits" since a year after a motor-car accident at the age of fourteen years, twenty-four years before admission to hospital.

History.—She had had an average of two to three fits per week since, on some days as many as six. The longest interval was three to four months. She would have a few seconds' warning, her right arm, leg and face would become stiff, and then unconsciousness would follow. She had often bitten her tongue and passed urine during attacks. Since the first fit she had noticed weakness of the right arm and leg, which had been much worse in the last three months. She had had pain in the right arm for three months.

Examination.—On admission to hospital she was garrulous and aggressive. Otherwise her mentality was not significantly impaired. An intracranial arterial bruit was best heard over the orbits and not completely silenced by compression of either carotid artery. There was right hemiparesis, but no sign of sensory changes.

Investigations.—The X-ray appearance of the skull was normal. Left percutaneous angiography showed a large cerebral angioma in the left hemisphere. Right percutaneous angiography showed filling of the upper medial portion of the left angioma.

Result.—No operation was performed. The effect of a course of deep X-ray therapy is to be observed.

CASE VIII.—A man (N.S.), aged seventy years, was admitted to the Alfred Hospital on October 18, 1949, under the care of Dr. Morris C. Davis.

First Symptom.—He complained of headaches and weakness for one month.

History.—He had fallen off his bicycle three months before admission. He had complained of weakness and headache for one month before admission. The relatives' observations were not available.

Examination.—He was drowsy, disorientated and unable to recall recent events. The level of consciousness varied from day to day in hospital. The plantar responses were extensor, but papilloedema was not present and there were no other unequivocal neurological signs.

Investigations.—X-ray examination of the skull showed a displacement of the pineal gland to the left. Right percutaneous angiography showed a displacement of vessels away from the skull wall, the appearance being that of subdural hæmatoma (Figure IV).

Operation.—A large right subdural clot and a small left subdural clot were both drained.

Result.—The patient recovered, and has reported by letter recently that he is very well.

CASE IX.—A woman (A.R.), aged fifty-two years, was admitted to the Alfred Hospital on April 6, 1949, under the care of Dr. L. B. Cox.

Presenting Feature.—She had had "post-traumatic" epilepsy for ten years.

History.—In retrospect she seemed to have had a few major attacks, interspersed with right-sided Jacksonian (motor) attacks. There had been periodic reduction of power in the right arm and leg, with recovery each time, for two years. The frequency of the fits had increased in the last weeks, and she was admitted with almost continuous right-sided motor epilepsy without loss of consciousness.

Examination.—Her blood pressure on admission to hospital was 240 millimetres of mercury, systolic, and 120 millimetres, diastolic. After control of the epilepsy she had right hemiparesis. There were no other signs.

Investigations.—The X-ray appearance of the skull was normal. The cerebro-spinal fluid contained no cells and the protein content was normal. Encephalography showed a deformity of the left lateral ventricle in the frontal region, and slight shift.

Result.—Operation was deferred because her hemiparesis again disappeared, she has severe hypertension, the tumour is unfavourably situated in the dominant hemisphere, and is very likely to be an invasive glioma. More recent air studies show the tumour to be enlarging.

CASE X.—A woman (C.R.), aged sixty years, was admitted to the Alfred Hospital on May 19, 1949, under the care of Dr. L. B. Cox.

First Symptom.—She had had buzzing in the left ear for ten months.

History.—The buzzing had persisted, and she had also had "tolling of bells" in the left ear for two weeks. She had staggered when walking for several months. She had had aching "neuralgia" in the left cheek for a few months, and numbness of the left side of the tongue. She had had "headaches like knives lately" behind the eyes, which did not last long and were eased with medicine.

Signs.—She had lateral and upward vertical nystagmus, hypalgesia of the left cheek and left side of the tongue, left-ear deafness, but no papilloedema.

Investigations.—X-ray examination of the skull with Stenver's views showed decalcification of the left internal auditory meatus, but no enlargement. The cerebro-spinal fluid contained 180 milligrammes *per centum* of protein. Caloric tests showed "diminished sensitivity of the left labyrinth".

Operation.—A left acoustic neuroma was completely removed.

FIGURE IV.

CASE XI.—A woman (J.B.), aged twenty-two years, was admitted to the Alfred Hospital on March 14, 1949, under the care of Dr. L. B. Cox.

First Symptom.—She had had dry retching in the mornings for six months before admission to hospital.

History.—She soon began to walk as if drunk and veer to the left. She had had deafness in the left ear for two months and difficulty in looking to the left. Her mouth became crooked, and she had occasional difficulty in swallowing.

Signs.—There was no papilloedema. There was nystagmus—coarse to the left, fine to the right, and vertical on upward gaze. There was left fifth nerve motor paresis, and the left corneal reflex was reduced. She had left lower motor neuron facial weakness; hearing was reduced in the left ear; the palate deviated to the right; left pharyngeal sensation was lost; there were mild left pyramidal signs. Her gait was unsteady, she walked on a wide base and veered to the left.

Investigations.—The X-ray appearance of the skull was normal. Caloric reactions showed her nystagmus to be unaffected by stimulation of either side.

Operation.—Exploration of the posterior fossa disclosed a brain stem tumour. A course of deep X-ray therapy was followed by a remarkable lessening in all signs, and she returned to work. In September, 1949, she suffered a rapid onset of headache, and papilloedema was found. She was readmitted to the Alfred Hospital, and died suddenly two weeks later with respiratory failure.

Autopsy.—A tumour one inch by one and a half inches by two and a half inches was found at autopsy, filling the fourth ventricle, and extending laterally into the left cerebellar hemisphere. The point of origin was not clear. Examination of a section showed a very cellular tumour, of glial origin.

CASE XII.—A woman (G.S.), aged sixty-three years, was admitted to the Alfred Hospital on March 21, 1949, under the care of Dr. L. B. Cox.

First Symptom.—She had had, for fifteen months, sudden severe headaches at the back of the head and neck followed by unconsciousness "if I throw my head back".

History.—Lately unconsciousness had occurred without headache if she suddenly threw her head back from a fixed position, for example, when hanging out the clothes. She would be "out to it" for a few minutes only, but would be unable to move for a while after "coming round". She had had sleepiness after an attack—or at "any time of the day or night"—for twelve months, and momentary unsteadiness while walking, for eight months. She had had nausea with headaches for two months, but had rarely vomited. The left ear had been deaf "for years".

Examination.—There were no physical signs. The history suggested a third ventricle tumour.

Investigations.—The X-ray appearance of the skull was normal. Lumbar puncture pressure was 170 millimetres of water, and the cerebro-spinal fluid contained no cells and a normal amount of protein. Air encephalography was performed, but no air entered the ventricles. A rounded mass was outlined by air in the posterior fossa.

Operation.—Ventriculography showed dilated ventricles, but no shift. Suboccipital craniotomy disclosed a translucent cyst, one and a half inches in diameter, containing clear fluid, lying between the cerebellar lobes and attached to the vermis. It was removed, some wall being left at the point of attachment. Examination of a section showed a fibrous tissue wall lined by flattened cells, the condition being possibly a meningeal cyst.

Result.—The result was satisfactory, and the patient's symptoms were relieved. She is now leading a normal life.

CASE XIII.—A boy (P.W.), aged three years, was admitted to the Alfred Hospital on September 27, 1949, under the care of Dr. L. B. Cox.

First Symptom.—He had had a "large head" since he was a baby.

History.—His head was gradually growing bigger. He had had "torticollis" after whooping-cough at the age of fifteen months, and was treated with a neck cage. His walking had been unsteady since the age of fifteen months, with a tendency to fall to the left. A squint was noticed at this time, and was blamed for the unsteadiness. His balance had been worse for two months before admission to hospital; he walked with his feet wide apart, but his "legs were not weak". He had had neither headache nor vomiting. The last few weeks he had been grizzly and irritable and listless, whereas previously he had been bright. Kindergarten reports had been excellent.

Examination.—He had a large head, bilateral papillœdema and gross cerebellar ataxia, and could not stand. There were no other signs.

Investigations.—X-ray examination of the skull showed a large head, with suture diastasis. Lumbar puncture pressure was 260 millimetres of fluid, and the cerebro-spinal fluid contained 60 milligrammes *per centum* of protein and no cells.

Operation.—Operation was perforce deferred owing to an infected scalp abrasion. There was considerable deterioration, and ventriculography one month later showed gross ventricular dilation with upward displacement of the fourth ventricle. Craniotomy disclosed a cellular tumour filling the greater part of a distended fourth ventricle and extending into the right cerebello-pontine angle. Examination of a section showed a tumour of the medulloblastoma type.

Summary.

1. The principles of diagnosis are briefly stated.

2. Some comments are made upon methods of investigation, with special reference to the nature of early symptoms and to the sequence in which the various methods of investigation are used.

3. The summaries of 13 case histories are given to exemplify early symptoms and the results of investigations.

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THE USE OF DI-HYDRO-ERGOTAMINE IN OBSTETRICS.[1]

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DI-HYDRO-ERGOTAMINE is one of a series of synthetic products prepared from the ergot or lysergic acid group of alkaloids by Stoll and Hoffman (1943). Though several others are of potential interest, to date only two have attained therapeutic popularity—methyl-ergometrine (methergine), which is a substitute for ergometrine, and di-hydro-ergotamine (marketed under the name of DHE 45), which has been used extensively and with success in the treatment of migraine (Horton, Peters and Blumenthal, 1945; Alvarez, 1947). Since August, 1949, the drug has been in use at the King George V Memorial Hospital for Mothers and Babies for treatment of prolonged labour in selected cases, particularly those in which the delay was associated with the type of dysfunction known as "incoordinate action of the uterus". There is no need to emphasize how much anxiety and distress can be caused by such a labour, nor to point out the not inconsiderable dangers to both mother and fœtus.

Up to the present management has been unsatisfactory. Cæsarean section, though often the wisest procedure, should not be necessary. The use of pitocin, whilst it certainly increases uterine activity, is often disappointing, and even in skilled hands and in small dosage, is not without danger. Pethidine is said to possess anti-spasmodic properties, but the effect is rarely dramatic. Except in cases of constriction ring dystocia, the remaining drugs that we use cause relief rather to the obstetrician than to the patient. It is no exaggeration to say that the use of drugs to facilitate dilatation of the cervix has been unsuccessful. Treatment in the long run consists of general nursing care and discreet sedation.

Hans Sauter, of Zurich (1948), suggested that heightened sympathetic nervous activity during labour was one of the most frequent factors in the causation of uterine dysfunction. He maintained that the effect was to raise the tone of the uterus as a whole—that is, of both the upper uterine segment and the lower segment and cervical zone; in other words, it tends to produce a condition identical with the inefficient type of labour known as "incoordinate action of the uterus" or "hypertonic uterine inertia"—a fairly common clinical entity. He suggested, therefore, that a suitable sympathicolytic should be of value in such cases, and, after trying several drugs, he selected di-hydro-ergotamine, reporting 30 successes in a series of 43 cases of hypertonia. Reist (1949), also of Zurich, has reported a similar series.

[1] Read on October 21, 1950, at the conference of Fellows and Members of the Royal College of Obstetricians and Gynæcologists in New South Wales.

Such a theory is in keeping with the well-worn adage "tense woman, tense cervix", with the ideas of Grantly Dick Read, and with the known effects on labour of spinal and caudal analgesia and perhaps of presacral neurectomy. It must be obvious to us all that there are both emotional and reflex inhibitions which can influence the course of labour. In fact, during the antenatal observations, we attempt to assess the likelihood or otherwise of a normal labour according to the psychological make-up of the patient. However, some of the most difficult and stubborn of labours are encountered in apparently emotionally stable individuals; but as a general rule such women, provided confidence has been established, have comparatively normal labours.

Pharmacology.

To be safe for use during labour, it is essential that the drug selected should have no action likely to have an adverse effect on either of the participants. In particular, uterine tonus must not be raised, and there must be no significant lowering or raising of the blood pressure.

The pharmacology of di-hydro-ergotamine is perhaps best described by contrasting it with ergotamine, which is typical of the lysergic acid alkaloid group. Chemically they differ only by one double-bond, but their pharmacological properties are quite distinct. The more important effects are shown in Table I, contrasted with those

TABLE I.

Pharmacological Properties.	Ergotamine.	Ergometrine.	Di-hydro-ergotamine.
Uterine stimulant	++	+++	o
Sympathicolytic (adrenergic-blocking)	+	o	+++
Vasoconstrictor	++	o	Compensated (slight vaso-dilatation)
Anti-migraine	+++	+	+++
Emetic	++	o	+
Gangrene producing (endothelial damage) toxic	++	o	o

of ergotamine and ergometrine. The prolonged "oxytocic" effect of ergot, which is extremely dangerous to a *fœtus in utero*, at least until delivery is almost completed, is lost in the dihydrogenation process. In some animals, in fact, the uterine effect is reversed, the drug being antagonistic to ergometrine (Rothlin, 1946-1947); this does not appear to be the case in the human, but further work will be necessary before we can state with certainty what the effects in the human parturient really are. Clinically there has been no suggestion of any interference with the third stage of labour.

The toxicity, as Table I shows, is very low. Enormous doses fail to produce gangrene in rats, and even vomiting it rare (Orth and Ritchie, 1947). The vasoconstrictor effect is slight, and is more than compensated for by the adrenergic-blocking action, the result being slight vasodilatation which is not sufficient to have a significant effect on the blood pressure. In laboratory animals, large doses have been given throughout pregnancy without apparent effect. The drug has been in use in the treatment of migraine for seven years, and its low toxicity in the human has been clearly demonstrated. Pregnant women suffering from migraine have been treated without complication. It must be emphasized that the doses used in migraine are several times greater than those we have been using, the dose we recommend for obstetric use being only one-quarter of an ampoule.

Clinical Trials.

The figures presented cover a period from August 17, 1949, to September 15, 1950, during which time 4294 mothers were confined in the hospital. For various experimental and therapeutic reasons we have administered one or more doses of the drug to upwards of 200 obstetric patients without observing any toxic effects. The majority were not suffering from delayed labour, many being patients on whom an attempt at induction of labour was performed. It was hoped that greater success might be achieved, but the results are difficult to assess and the drug is still under trial.

For the purpose of this paper a series of 67 prolonged labours has been analysed. This comprises the patients who first received the drug after being in definite labour for more than twenty-four hours, and in whom there was no physical obstruction to labour; several cases of successful trial labour in a small pelvis are included. Two cases only of obstructed labour have been excluded—a brow presentation and an outlet contraction. All but five of the patients were *primigravidæ*. Both public and private patients are included, and more than 20 members of the honorary medical staff have contributed clinical material. Thus the selection of cases and the timing of administration have varied, and with greater experience better results may well be obtained. In general the drug has been given when there has been evidence of slowing or cessation of progress, and it should not be given simply because the labour is slower than usual. It is not suggested that all 67 cases were classical examples of uterine inertia, and several patients were included who, in our opinion, did not require the drug; but the average duration of labour for the whole series, excluding the two failures in which Cæsarean section was necessary, was more than 54 hours. One of the Cæsarean section patients was aged forty-one years.

At present the drug is marketed in one-millilitre ampoules which contain one milligramme of di-hydro-ergotamine. The dosage used is 0·25 milligramme (0·25 millilitre) given by intramuscular injection. It may be repeated in safety after four hours, and is worth repeating even when there has been little or no response to the first dose; in a few cases the response to a second dose has been dramatic. In 47 of the cases under review only a single dose was given, and in only one instance was a useful response obtained when more than two injections were considered necessary. Clinical fœtal distress has never been observed to follow, but in one case it appeared temporarily to be relieved after the injection, only to recur later, the infant dying soon after delivery. In all the series there were five stillbirths and three neonatal deaths, a total wastage of eight in 67 cases. In no instance, as the following brief summaries show, is there any evident association between the death of the baby and the therapy.

The five stillbirths were as follows: (i) Difficult manual rotation and forceps delivery were required. Fœtal heart sounds were heard just before delivery. No autopsy was performed. (ii) Manual rotation and forceps delivery were required three hours after the administration of di-hydro-ergotamine. Fœtal heart sounds were irregular twenty minutes before delivery. The autopsy finding was asphyxia. (iii) The autopsy finding was intrauterine staphylococcal pneumonia. (iv) Fœtal distress was noted during the second stage of labour. The autopsy finding was asphyxia. (v) Fœtal distress was present before di-hydro-ergotamine was given. There was a good effect on the progress of labour, but the fœtal heart sounds disappeared one and three-quarter hours later. No autopsy was performed.

The three neonatal deaths were as follows: (i) The infant was well at birth, but died on the third day from hæmorrhagic disease of the newborn. (ii) A multiple pregnancy was present, with preeclampsia. A difficult forceps delivery was performed twenty-one hours after the administration of di-hydro-ergotamine. The autopsy finding was asphyxia. (iii) Fœtal distress was present before di-hydro-ergotamine was given. There was temporary relief followed by forceps delivery. The autopsy finding was asphyxia *plus* intracranial hæmorrhage.

We believe that the drug is safe, used as we have used it; but only when many more patients have been treated can there be absolute certainty on this point. On the other hand, several babies lived whose chance of survival would otherwise have appeared to be remote. Whilst we have

not used a larger initial dose than 0·25 milligramme, a warning against larger doses is warranted. Doses of 0·5 milligramme have been used both in Switzerland (Sauter, 1948; Reist, 1949) and in one case at least in Sydney. Whilst no disasters have been reported, in several instances alarming contractions have followed. In one of our own cases, powerful frequent contractions followed the smaller dose, enough to cause some concern, but not fœtal distress. We have used the drug in two cases only of constriction ring, but without effect, though one patient responded rapidly to adrenaline. The third stage of labour has been surprisingly normal for a series of long labours. In no case was immediate blood transfusion necessary for post-partum hæmorrhage.

The drug appears to be of value in the following types of case: (i) the hypertonic uterus, including cervical dystocia; in such cases it may be given early in labour; (ii) the sluggish labour which often follows induction; (iii) atonic uterine inertia; in these cases the response is less dramatic, but the drug is well worth a trial.

It probably has a place in other cases in which acceleration of labour is justified, but on normal labour the effect, if any, is slight. Its value in induction of labour is open to question. It may be used, when the indications are present, in breech presentation, in labour with multiple fœtuses and in occipito-posterior presentations, and it may be combined with pitocin if this drug is used to augment labour.

However, if good results are to be obtained the following conditions should be fulfilled: (i) The uterus must be contracting actively. (ii) The patient must not be nearing exhaustion. Such a state should be treated first by sedation, di-hydro-ergotamine being given after she awakes if it is required at all. (iii) The cervix should be taken up and be showing some signs of dilatation. If the drug is given very early, success is less likely to follow. (iv) General care of the patient is still of first importance.

Nutrition, sedation and care of the bladder and bowels are essential, as is accurate obstetric diagnosis of position and presentation. The possibility of constriction ring must not be forgotten.

It is extremely difficult to present the results of treatment of dystocia. Many known and unknown factors are concerned in labour, and dramatic changes may occur quite apart from any treatment at all, or after, for example, the giving of an enema. A controlled statistical experiment is not practicable. The clinical record of each case has been summarized and carefully considered, particularly with regard to alterations in the nature of the contractions and changes in the dilatation of the cervix during the four hours following the injection. The apparent result has then been assessed arbitrarily as shown in Table II. In order to minimize personal bias, the assistance of Dr. J. M. Farrar was sought and each assessment was discussed carefully. The figures for cases in which forty-eight hours of labour preceded the injection are shown for comparison. These figures are probably of less value, as most cases of prolonged labour cause such concern before forty-eight hours have elapsed that the drug is usually given earlier. The late cases, therefore, tend to be emergency cases (some patients being exhausted), and the milder, atonic types which have not caused much concern. A table showing greater detail of the first 43 cases treated has already been published (Gill and Farrar, 1950). Table III summarizes the mode of delivery of the patients, and it is interesting to note that 29 of the 67 patients delivered spontaneously.

It was mentioned earlier that a number of patients had received the drug before twenty-four hours of labour had elapsed. Some of these were undoubtedly suffering from early "incoordinate action of the uterus". These were excluded, as a clear definition of delayed labour was necessary, and the twenty-four hour period was chosen. This has resulted in the exclusion of at least five severe and distressing cases in which the treatment was a total failure; but it also excludes a much larger number of apparent successes. It has not been possible to predict the case in which the response to the drug will be disappointing; several such cases have been those which seemed, in the light of our small experience, to be ideally suitable. However, if the drug is used in accordance with the indications given earlier and in the dosage advised, useful results can be expected in about 75% of cases.

TABLE II.

Apparent Effect on Labour.[1]

Effect.	Twenty-four Hours of Labour before First Dose.		Forty-eight Hours of Labour before First Dose.	
Excellent	13	53	3	11
Good	31		6	
Fair	9		2	
Doubtful	7	14	2	4
None	7		2	
Total	67		15	

[1] Average duration of labour before first dose, 42·3 hours; average duration of labour after administration of DHE 45, 12·2 hours; average duration of labour, 54·5 hours.

The Effect of Di-hydro-ergotamine in Labour.

After the administration of di-hydro-ergotamine there is usually a delay of half an hour or more before any change is evident, though occasionally the effect is almost instantaneous. Most often both patient and observer note an increase in the strength of the contractions, the patient often feeling that she is at last making headway. She has occasionally been distressed by increased sensation of pain and suitable sedation may be indicated; on the other hand, in several instances the drug has acted like a sedative, and a tense, excited, non-cooperative woman has calmed down as her labour has become normal and efficient. Relaxation between contractions is usually much improved in hypertonic labours. In the patient with a tight ring-like cervix, which may even contract with each pain, the dilatation may be most dramatic; on several occasions, in fact, the baby has been "born before arrival". In the atonic group, the response generally is less dramatic, but there is often a considerable improvement in the strength of the contractions. It must be repeated, however, that the drug seems to be of no value when the uterus is entirely inactive. In some cases there may be no evident change in the pains, but examination after two to three hours may reveal a great improvement in the dilatation of the cervix.

TABLE III.

Mode of Delivery.

Type of Delivery.	Number.
Spontaneous (vertex presentation)	29
Rotation and application of forceps	16
Simple forceps application	16
Breech	3
Delivery of multiple fœtuses	1
Cæsarean section	2
Total	67

Perhaps two clinical histories can be quoted as examples.

Mrs. P. was a *primigravida* who commenced her labour some six weeks before term, the membranes rupturing early. She was a nervous woman with high uterine tone and weak, distressing contractions. On her admission to hospital the cervix was dilated to admit two fingers, and thirty-six hours later its condition had not altered. Di-hydro-ergotamine was then given; the amplitude of the contractions increased, relaxation between them improved, and four hours later the degree of dilatation was four fingers. The dose of di-hydro-ergotamine was repeated, and within six and a half hours she was in the second stage of labour. The baby survived, with a ring of pressure necrosis around a *caput succedaneum*.

Mrs. G. was also a *primigravida*, admitted to hospital in early labour. The fœtal head was high and the cervix was dilated to admit one finger. Twenty-four hours later the condition was unchanged, despite fair contractions. During the next twelve hours the head advanced a little, and the degree of dilatation had reached two fingers. Four hours later the condition was again unchanged, and di-hydro-ergotamine was given, forty hours after labour had commenced. After an hour and a quarter the cervix was half-dilated with strong contractions, and two and a half hours later the baby was delivered spontaneously.

Conclusion.

We feel that di-hydro-ergotamine is a valuable addition to our obstetrical armamentarium, to be used in conjunction with the methods of treatment that we already employ. Sedation, the catheter, the forceps and the scalpel all have their place, though it is hoped that the place of the scalpel will be lessened.

Summary.

1. Sauter's theory of the causation of incoordinate action of the uterus is presented and discussed.

2. The pharmacology of di-hydro-ergotamine is summarized.

3. The results of the treatment in 67 cases of delayed labour with di-hydro-ergotamine are reported, an apparently useful result being recorded in 53 cases.

4. Recommendations are made as to the dosage and indications for the use of the drug.

Acknowledgements.

I should like to express my thanks to my colleagues of the honorary medical staff of the King George V Hospital for permitting access to the necessary clinical material and for allowing the use of the records of their private patients. I should thank also the resident medical staff and the nursing staff for their keen cooperation, and in particular Dr. J. M. Farrar for much assistance, including help with the assessment of results. My thanks are also due to Dr. Z. Enis and Dr. H. Frant for help in translation.

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Reviews.

PSYCHOANALYSIS.

THE "Freud: Dictionary of Psychoanalysis"[1] consists of an alphabetically arranged list of Freud's technical terms, largely as defined in his own writings, edited by Nandor Fodor and Frank Gaynor; the former being an "Associate of the Association for the Advancement of Psychotherapy" and the latter co-author of the "Dictionary of Industrial Psychology".

It is a valuable book, but a warning is advisable. In the introduction the editors suggest that what is written consists of exact quotations, but a sentence under the heading of "Sexuality in Childhood" is not only a paraphrase; it is an incorrect statement. The editors write: "The sexual activity of the child, however, does not develop in the same measure as his other functions; but merges first into the so-called latency period from the age of three to the age of five years." The corresponding sentence on page 109 of Freud's "Three Essays in the Theory of Sexuality", Imago Publishing Company, London, reads: The sexual activity of children, however, does not, it appeared, develop pari passu with their other functions, but, after a short period of efflorescence from the ages of two to five, enters upon the so-called period of latency." Though the editors' rendering incorrectly sets the latency period before five years of age, this mistake is not made under the heading of "Latency Period", which is defined as: "The period of life from the end of the fourth year to the first manifestations of puberty at about eleven."

The only other definite mistake noticed was a misprint in the "Key of References", but before another edition is published paraphrasing should be clearly distinguished from quotation. In addition, though the editors state that page references have been omitted because of "the confusion which the plurality of editions would create", the value of the dictionary would have been much enhanced if the page reference of each entry for all editions had been inserted. Finally, the terms catharsis, imago, introjection and symbolism have been omitted, and the definitive passages for ambivalence, Œdipus complex and projection are ill-chosen or require amplification by other entries.

Despite these criticisms we agree with the laudatory opinion of the well-known psychoanalyst Theodor Reik who writes in the preface: "The editors of the book . . . are willing, no, more than this, they are eager to augment and correct it, to fill gaps in later editions which will become necessary because the merits of such a work will soon be recognized by the students of psychoanalysis."

[1] "Freud: Dictionary of Psychoanalysis", edited by N. Fodor and F. Gaynor, with a preface by T. Reik; 1950. New York: Philosophical Library. 8½" × 5½", pp. 228. Price: $3.75.

OCCUPATIONAL THERAPY.

A COMPREHENSIVE TREATISE on the subject, written by physicians for physicians, is "Occupational Therapy: Principles and Practice", by William Rush Denton and Sidney Light, the past and present editors of the journal *Occupational Therapy and Rehabilitation*. A chapter devoted to the history of the subject tells that this form of therapy has been practised since ancient times for the mentally ill, but it is largely as a result of the last World War that its scope has been so greatly enlarged, and now it may be defined as "any activity, mental or physical, definitely prescribed and guided for the distinct purpose of contributing to and hastening recovery from disease or injury".

Acknowledged specialists in their own fields have contributed chapters; thus Paul D. White writes fully on occupational therapy in heart disease, giving a balanced account of all that can be done for patients with varying amounts of cardiac reserve to call upon for their activities. Phyllis Lyttleton writes on therapy for "amputees", bearing in mind the importance of the psychological approach to this phase of treatment. Bibliotherapy in neuropsychiatry is discussed by Jerome M. Schneck and drama therapy by Alfred P. Solomon, to mention some of the various chapters. However, every particular form of occupational therapy for the maladies of both the body and the mind are completely described. Most doctors would have liked to see more detailed descriptions of the scope of occupational therapy in rehabilitating patients with orthopædic disabilities in industry, and the application of modifications to factory machinery to enable them to be operated by the physically handicapped, for while various forms of kinetic and psychological therapy can be initiated successfully while the patient is in a hospital or sanatorium, its value will be lessened largely unless scope is given for the patient to return into the community as a useful citizen. It can be seen readily that the greatest problem associated with occupational therapy is that of rehabilitation, but present indications are that this aspect is developing all the time.

[1] "Occupational Therapy: Principles and Practice", edited by William Rush Denton, junior, M.D., and Sidney Light, M.D.; 1950. Illinois: Charles C. Thomas (Publishers). Oxford: Blackwell Scientific Publications, Limited. 9" × 6", pp. 248, with a few illustrations. Price: 45s.

The Medical Journal of Australia

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CORONARY DISEASE AND CABBAGES.

RUMOUR has it that a small boy once translated "*pax in bello*" as meaning "freedom from indigestion". While we may acquit the lad of any philosophical insight into the causation of certain gastric disorders, we know that absence of commotion, due to war or to other conditions causing anxiety, or even a placid temperament in the presence of disturbing events is favourable to gastric comfort. There is some justification for the view that a patient with peptic ulcer is more appropriately treated by a psychiatrist than by a specialist in internal medicine. Indeed, the wise physician is one who prefaces the investigation of every patient by an inquiry into his mental state, whether it is one of peace or of anxiety. Nowhere is this more necessary at the present time than in the investigation and treatment of patients suffering from coronary occlusion, a pathological condition claiming many of its victims from among, or more correctly frequently manifested in, the ranks of the medical profession. Every senior medical practitioner will agree that coronary occlusion is much commoner than it used to be, and many will consent to the view that it is more likely to be encountered among those who work with their brains rather than with their muscles. Apparently this is open to some question. In a series of 1620 attacks of coronary occlusion investigated by A. M. Masters, S. Dack and H. L. Jaffe and discussed in this journal on January 11, 1941, 36% of the patients were manual workers and labourers, 9·5% were "white collar and office workers", 8·5% were professional persons, 11% were business men, 20% were housewives and 9·5% were "retired". W. M. Yater and five co-workers in 1948 discussed 866 cases of coronary artery disease occurring in servicemen under forty years of age.[1] They refer to the occupation of the men before they joined the services and state that there appeared to be a tendency for the men to have been engaged in the less physically arduous occupations, such as clerical service, professional and supervisory rather than in factory, labour and farm occupations. In the Carey Coombs prize essay for 1949 of the University of Bristol, I. McD. G. Stewart has dealt with coronary disease and modern stress.[2] Stewart quotes figures from the Registrar-General's Department. In a comparison of occupational groups in which the figure 100 is taken to represent the average death rate from coronary disease for all males aged twenty to sixty-five years, the following figures are given: agricultural workers, 32; coalminers below ground, 40; banking and insurance officials, 183; Anglican clergy, 218; physicians and surgeons, 368. As a matter of fact it is the publication of Stewart's paper which has prompted our reference to this subject. Robert Platt, of the Department of Medicine in the University of Manchester, has discussed Stewart's article,[3] and he points out that the Registrar-General's figures depend for their accuracy on the accuracy of the material from which they are compiled, namely, death certificates. He points out that the figures given by Stewart relate to the period 1930-1932, and that "coronary thrombosis as a cause of death was not commonly diagnosed even by experienced physicians until about 1930". He also quotes the following statement by the Registrar-General:

> . . . degenerative disease in the heart affects all classes of males to much the same extent, but whereas among men whose social conditions are most favourable it tends to express itself as angina pectoris or coronary disease, at the other end of the scale it tends to take forms described on death certificates as myocarditis or myocardial or cardio-vascular degeneration.

Platt holds that without this statement most of the figures quoted by Stewart are very nearly meaningless. Without going further into the rights or wrongs of any of these divergent views, we may conclude that when we state our beliefs on the incidence of coronary occlusion, we must remember that they are based on impressions, well grounded perhaps, but still not proven as facts.

With the foregoing statement in mind, we may turn to the main theme of Stewart's essay—that modern stress has a selective action on the coronary arteries of certain types of person. He points out that if it could be proved that a particular form of stress might lead to metabolic change, perhaps to increased blood pressure, an important step might be taken towards finding a cause for generalized atheroma. Even so, there would still require to be explained the strange predilection by which atheroma develops disproportionately in the coronary vessels, arising there sometimes in the total absence of lesions elsewhere. "The selectivity of the pathological change is the kernel of the problem." He admits that the solution must await the results of further research by biochemists and histologists. In the meantime empirical views have a certain amount of value. Stewart asks whether there has developed during the last few decades, as a result of the increased "pace" of life, any special stress which bears chiefly on the aged male section of the community. He believes that there has and that its influence is becoming more widespread. "The essence of this stress is that it confronts its victim with an opposition which he feels himself driven to combat, and capable of surmounting, but only at the cost of extreme and long-continued effort." The corroding effect of this kind of endeavour is not usually revealed. Conditions which are outside the control of the individual do not produce the same tension, and it

[1] *American Heart Journal*, Volume XXXVI, 1948, pages 334, 481 and 683.

[2] *The Lancet*, December 23, 1950.

[3] *The Lancet*, January 6, 1951.

is undoubtedly true that not all temperaments are susceptible to modern stress. Stewart paints a somewhat slick picture of the worker who puts his trust in collective action and waits for something to turn up, whose standards and values are cooperative and not competitive. The picture is not entirely convincing, but it reads very well. "Whatever the size of his pay-packet he makes a point of spending all that he earns" sounds as though the statement was being made to fit as an explanation and did not come naturally. After all most people today have to spend all they earn if they wish to pay their way, though many of these are naturally more improvident than others. The improvident, like other groups of men that could be named, do not all appear improvident from choice. Many people are so placed that they have very little with which to be provident. Those who have an opportunity to fight for advancement and to achieve something in the intellectual, business or social sphere, would be those grouped by Stewart and those who agree with him, as likely candidates for coronary occlusion. Whether, Stewart's idea being correct, they ever achieve that pathological distinction or not will depend in large measure on their temperaments. The placid person will take success or defeat with equanimity. His opposite in type will worry even though he is successful—fearing perhaps that one greater than he will come along to supersede him. Not every man can "by taking thought add one cubit unto his stature" and stay contented with what he has done. A business man, discussing this subject recently, said that in the bygone days the leader or administrator was the psychologist and knew how to treat, for the advantage which he wished to gain, those whom he led or whose employment he had to administer. Nowadays everyone studies psychology and Jack is as good a psychologist as his master or leader. The non-placid master or leader who knows this lets his imagination run away with him. Again we know what a "cold war" means in international affairs. The same kind of warfare exists in many different corners of community life, and it must have its effect on the susceptible.

Stewart's article is useful in that it turns our attention to an important aspect of an important subject. The importance of the subject to medical practitioners was stated with bluntness to a medical audience by a speaker who pleaded for attention and interest because 25% of those present would probably die of coronary occlusion. If Stewart's admittedly empirical statements were accepted holus-bolus we should have to choose between a coronary death and a life as a cabbage. Cabbage men have been described in this journal as taking life as it comes and asking no reasons why (see THE MEDICAL JOURNAL OF AUSTRALIA, February 22, 1941, page 239). The choice for intelligent people would not be difficult—who would not spurn a vegetative existence for a life of adventure and striving, maybe for the unattainable, even if conclusion came by occlusion? The thing to do is to cultivate equanimity. The attempt should be made, and to spur us on we have some lines from Rudyard Kipling's "If":

> If you can dream—and not make dreams your master;
> If you can think—and not make thoughts your aim;
> If you can meet with Triumph and Disaster
> And treat those two impostors just the same;
> . . . . . .
> Yours is the Earth and everything that's in it,
> And—which is more—you'll be a Man, my son!

Current Comment.

CORTISONE.

THE presentation of the condensed facts about cortisone in a special lecture by the distinguished biochemist who produced the now world famous compound E is worth careful study. Edward C. Kendall, in a John Phillips Memorial Lecture delivered at Boston before a meeting of the American College of Physicians, points out that there are two apparently widely separated aspects of the research, one largely clinical, concerned with the so-called collagen diseases, and the other biochemical, concerned with the nature of the adrenal cortical hormones.[1] The collaboration which made possible the striking and stimulating results of this work has been noteworthy, and we owe much, not only to Kendall, but also to Philip S. Hench, who has made many contributions to the study of the rheumatic group of diseases. We have been familiar for a number of years with the striking, though incomplete, amelioration of Addison's disease by making use of the known facts about the influence of the adrenal cortex on electrolyte balance, and the relative failure of desoxycorticosterone in this disease. It is interesting to reflect that compound E, a white crystalline substance isolated from the gland, was known fifteen years ago. It is still more interesting to read that Kendall, with a genuine conviction that this compound held essential secrets of the adrenal gland, continued to pour his energy into its production. Another substance, compound A, which had not been proved to be qualitatively different from E, was prepared in larger amounts, but its clinical use in Addison's disease was disappointing. There seemed little to encourage attempts to produce compound E in reasonable quantity, at this stage; in 1946, a method was discovered by which the yield of compound E was increased one hundredfold by the use of a new technique for converting A into E. This enabled Merck and Company to produce a few grammes of compound E, and this firm then thought it advisable to confer with a group of clinicians to decide how the substance could best be used. Kendall remarks that the compounds A and E seemed doomed to be added to the discarded drugs, and no newspaper reporters waited to learn the result of the meeting. The fate of compound E, however, depended largely on the results of discussions between Hench and Kendall. It will be recalled that it was Hench who pointed out the possible reversible nature of rheumatoid arthritis, since remissions were observed during attacks of jaundice and during pregnancy, and that he had studied exhaustively the effects of therapy of various conditions by foreign protein, and had emphasized the widespread bodily reactions which occur under this stimulus. After all, Selye is not the only physician who has attempted to integrate the struggles of our complicated metabolic machine against physical and chemical insult. Modern study of the group of diseases usually now known as the collagen diseases has gone much farther than the descriptions *ab externo* of the older clinicians. Kendall does not enlarge on the arguments which led to the use of compound E in rheumatoid arthritis, but he tells us that this decision had really been made seven years earlier. The reasons for its tardy clinical trial were the difficulty in obtaining enough of the substance, which had been to some extent overcome, and also the slowness of absorption of the acetate salts of the substance. Further work led to the separation of compound E from its acetate, and to another most important detail. This was the adoption of 100 milligrammes as the daily dose, and its injection intramuscularly after preparation of the crystals by fine grinding to a powder. This was important, as it secured slow absorption and simulated the natural release of the substance from the gland. It is now quite unnecessary to describe the sensational success of this treatment, or the curious and sometimes disturbing side effects. The extraordinarily wide range of the other conditions for which compound E has been used is also a most stimulating subject, in which there appears to be far more than we

[1] *Annals of Internal Medicine*, October, 1950.

can understand at present. Confusion with vitamin E occurred soon after the publicizing of this work, and as this was undesirable in the interests of the public, Kendall and Hench shortened the chemical name of compound E from 11-dehydro-17-hydroxycorticosterone to cortisone. In his lecture Kendall speculates to some extent on the mode of action of this extraordinary substance. It does not appear to be a stimulator of the metabolic rate, nor does it initiate striking chemical changes in the bodily functions. It does not appear that the rheumatic affections are due to a deficiency of adrenal secretion, though prolonged administration of cortisone will cause atrophy of the cortex of the adrenal gland. The most obvious result of the success of this therapeutic measure has been the search for other substances which might be equally effective, but perhaps without the same side effects, and with the advantage of being easy and cheap to produce. This dream has not yet come true, though production of cortisone is a simpler problem than it was.

The story of cortisone is one of the most fascinating in modern medicine; it illustrates the possible rewards of great ability, tireless patience and industry regardless of an immediate objective, great insight and imagination, and admirable team work. All will surely agree that in the future application of this potent substance and others which will come after it should be correctly controlled, and that biddings of both science and humanism must be followed.

APPENDICITIS.

ALTHOUGH the broad picture of appendicitis has changed somewhat and its attendant dangers have lessened with the changes that antibiotics, supportive therapy and the rest have brought to clinical surgery, it remains of major practical importance. An investigation carried out by G. E. Moloney, W. T. Russell and D. C. Wilson,[1] based on Registrar-General's reports and on experience at the Radcliffe Infirmary, Oxford, emphasizes that there are problems associated with appendicitis still unsolved. It is estimated that some 60,000 cases of the disease occur in England and Wales each year (approximately one case among every 700 of the population), and despite progressive reduction in the death rate since 1920, 867 male subjects and 668 female subjects died as a result of appendicitis in 1946. Peaks in the age mortality occur between five and fourteen years and after fifty-five years; in the youthful period the peak is more distinct for boys, and the death rate for boys under five years in 1945-1946 was still equal to that in 1920-1922. There is suggestive evidence that the incidence of the disease is greater in male than in female subjects. A higher death rate in rural than in urban areas is as might be expected, but it is surprising to find (and no explanation is apparent) that the mortality for male subjects and for married women is greater in the higher economic grades of the population than in the lower; it is suggested that the reason may lie in dietary habits, but the finding needs further investigation. A comparison of the fatalities in the Radcliffe Infirmary series (1945-1948) with those in a series reported by Grey Turner in 1938 (1900-1934) reveals the most striking difference to be in connexion with the complication of general peritonitis; Grey Turner's figure was 29·2%, the Radcliffe Infirmary figure was 6·2%. It is interesting to note that in a series of 217 appendicectomies performed at King's College Hospital, London, between February, 1947, and August 31, 1949, and reported by Sir Cecil Wakeley and P. Childs,[2] there were no deaths, although general peritonitis was present in 17 of the 168 cases in which appendicectomy was performed as an emergency operation; Wakeley and Childs are strongly opposed to expectant treatment, and used it for a short time only in three cases—two of abscess and one of appendix mass. Their opposition to expectant treatment is supported by their results and by the Radcliffe Infirmary experience. Moloney, Russell and Wilson quote J. B. Murphy's caution, in 1916, that "early operation is the only safe practice". Subsequently, expectant treatment came into vogue and had a long and not unjustified popularity. However, modern advances in antibacterial and supportive therapy have changed the operational outlook, and delay is seldom defensible. Of 1027 cases in the Radcliffe Infirmary series in which the necessary information was included in the notes, in 75·5% the patients came to operation within forty-eight hours of the first symptoms. While 83% of the patients were in hospital within forty-eight hours, 25% of these already had complications. Of 175 patients treated after forty-eight hours, 57% had conditions graded as "severe". In 143 cases (14%) delay was greater than seventy-two hours; this included all but three of the fifteen fatal cases. At the other end of the scale 480 patients had a history of less than twenty-four hours' duration, yet 46 had flank or pelvic peritonitis, 25 had general peritonitis (one died), and nine had localized abscess; 164 allegedly had a history of less than twelve hours' duration, yet 22 of these already had flank, pelvic or diffuse peritonitis. A brief period of symptoms is thus no guarantee that the condition is not well advanced; to delay operation is dangerous. The evidence from the Radcliffe Infirmary series strongly supported the use of chemotherapy (sulphonamides and penicillin) in all cases in which inflammation has extended to the peritoneum, and on the value of this and of gastro-intestinal rest and intravenous fluid administration in the presence of complications there will be little dispute. On the indications for drainage there is less agreement. Wakeley and Childs always drain the wound if there is danger of contamination, but they consider that the peritoneal cavity should never be drained if the appendix has been removed; with late general peritonitis they place a drainage tube in the pelvis and a stab drain in the right iliac fossa and defer appendicectomy; with an appendix abscess they defer appendicectomy if the appendix is not readily accessible, and only then drain the abscess cavity. Moloney, Russell and Wilson have concluded that chemotherapy has largely removed the necessity for drainage, excepting when oozing of blood at operation has been considerable, when a chronic thick-walled abscess occurs, and when closure of the appendicular stump is uncertain (the caecum is then drained); they consider generally inadvisable the use of multiple drains, and find little virtue in wound drainage. There is much more detail in these papers that surgeons will wish to study for themselves in the light of their own experience. It is certainly evident that the approach to appendicitis, even with severe complications, has been much clarified and the outlook improved, though certain problems remain.

[1] *The British Journal of Surgery*, July, 1950.

[2] *British Medical Journal*, December 16, 1950.

FIFTY YEARS OF MEDICAL PROGRESS.

MOST of our readers also receive the *British Medical Journal*, and they will recall with pleasure the issue of that journal for January 7, 1950, which was devoted to a survey of medical progress between January 1, 1900, and December 31, 1949. The articles of that issue have now been published in book form.[1] The leading articles occupy the first chapter, and each of the 18 contributed articles has a chapter to itself. An index has been added, as well as a preface by Hugh Clegg, the editor of the *British Medical Journal*. Clegg remarks that we all knew in a vague sort of way that medical science, and so medical practice, had made big strides forward; but when the story came to be told, the width and depth of the advance came as a surprise to not a few. It is good, then, that this fine record should have permanent form and that the printing, illustrating and general set-up of the volume should be, as they are, worthy of it. The progress and its record do honour to our profession.

[1] "Fifty Years of Medicine", a symposium from the British Medical Journal; 1950. London: British Medical Association. 9½" × 6", pp. 344, with many illustrations. Price: 15s.

Abstracts from Medical Literature.

THERAPEUTICS.

ACTH and Acute Leuchæmia.

L. W. KINSELL *et alii* (*The Journal of the American Medical Association*, October 21, 1950) describe the treatment of a patient with monocytic leuchæmia with adrenocorticotropic hormone. The patient, a woman, aged fifty-six years, with acute leuchæmia, was treated by transfusion, and later with 25 milligrammes of ACTH given every six hours. For a week there was improvement, and the dose was decreased for some days; then the original dose was repeated. Progressive elevation of the blood sugar content led to a reduction of dosage again to 20 milligrammes every six hours. Ecchymoses and infections developed. "Chloromycetin", rutin and ascorbic acid were given. Blood transfusions were given freely throughout. The patient remained well for three months and eventually resumed her normal life. The blood count also became normal. Various explanations are offered for this unusual result of the use of ACTH.

Carcinoma of the Prostate Gland.

L. R. REYNOLDS, T. L. SCHULTE AND H. J. HAMMER (*Archives of Surgery*, September, 1950) consider that their results with conservative management of patients having carcinoma of the prostate gland have been encouraging. Diethylstilbœstrol was given orally to 104 patients when the diagnosis was first established. Originally the daily dose was three milligrammes or less, but for the past five years five milligrammes of the drug have been given once daily. Dosage was increased if the symptoms warranted or if metastasis became apparent. Fifty-six of the patients underwent transurethral resection for obstruction of the bladder neck. Lack of response to oral antiandrogenic therapy was unusual, and relapses, while encountered, were not as common as popular opinion indicated. The average survival period for all patients from the time of treatment until the time of this study was nearly thirty-four months. Twenty-two patients survived more than five years, but 65 patients now living have been under treatment for less than five years. This suggests that the number surviving for more than five years will appreciably exceed 21·2% in the future.

"Chloromycetin" in Surgical Infections.

W. A. ALTEMEIER AND J. GIUSEFFI (*Surgery, Gynecology and Obstetrics*, May, 1950) have studied the effect of "Chloromycetin" in a series of conditions due to various organisms and consider that it is a chemotherapeutic agent of considerable value in the management of surgical infections. They state that the toxicity is low and the effective dose for the majority of surgical infections varies between 25 and 100 milligrammes per kilogram of body weight per day when given by mouth. It can be used as a rectal suppository when the dose is increased by 30%. The interval between doses is recommended as four hours in severe infections and as six, eight or twelve hours in less severe infections. "Chloromycetin" is particularly valuable in the management of penicillin-resistant pyogenic infections, and in mixed infections it appears to be superior to penicillin, streptomycin or sulphadiazine. Bacterial resistance may occur during or after treatment. The fundamental surgical principles of early treatment—rest, adequate external drainage and general supportive treatment—remain as important as ever.

Aureomycin Therapy in Acute Viral Hepatitis.

JAMES M. SHAFFER, JOHN D. FARQUHAR, JOSEPH STOKES, JUNIOR, AND VICTOR M. SBOROV (*The American Journal of the Medical Sciences*, July, 1950) state that aureomycin was administered orally in doses of two or four grammes daily for six or ten days to three groups of patients (37 individuals in all) with acute viral hepatitis with jaundice. Control patients (37) received the same routine management without aureomycin. The duration of abnormal liver function was measured by an assemblage of hepatic function tests performed at frequent intervals. Comparison of the three groups has shown no significant difference in the average duration of jaundice, bilirubinuria, or positive results from flocculation tests, or in the clinical picture of the acute and convalescent phases of the disease, between those receiving aureomycin and the controls. The average duration of positive results from flocculation tests and elevated thymol turbidity was shorter in one treated group of adults than in the controls. Study of a larger series of cases will be necessary to evaluate this apparent difference.

Curare.

K. R. UNNA *et alii* (*The Journal of the American Medical Association*, October 7, 1950) discuss the evaluation of curarizing agents in man. They state that the first preparations introduced were purified *Chondodendron tomentosum* extract ("Intocostrin") and *d*-tubocurarine chloride, the natural alkaloid; other preparations, decamethonium (which is decamethylenebis (trimethylammonium) or "Syncurine" or C10) and "Flaxedil" are synthetic compounds recently introduced. These agents will paralyse skeletal muscles of the face and neck, then the muscles of the trunk and extremities; large doses will paralyse the respiratory muscles and cause death by asphyxiation. The latter is a danger with all curarizing agents. Investigations were conducted on male volunteers. Full examination of the patient was made, the strength of the grip of the subject's left hand was estimated, and then the curarizing drug was injected intravenously in ninety seconds. Forty-five seconds after the beginning of the injection, heavy eyelids and transient diplopia were observed, the facial, neck, back and extremity muscles became relaxed, the pharynx and jaw muscles were paralysed, and difficulty in swallowing was noted. Four agents were tested: tubocurarine chloride (average dose nine milligrammes), dimethyl-tubocurarine iodide (four milligrammes), decamethonium bromide (two and a quarter milligrammes) and "Flaxedil" (48 milligrammes). The last drug produced the most powerful effect, but variability in response to the drug was pronounced. This drug also affected the respiratory muscles with paralysis earlier than the other drugs. Tubocurarine derivatives gave a more prolonged action, and repeated doses of these drugs were cumulative when given at intervals of forty-five minutes. Repeated doses of decamethonium bromide were not cumulative. Neostigmine methylsulphate mitigates but does not completely abolish the effects of a subsequent injection of tubocurarine chloride. No effective antidote to decamethonium bromide in man is known. Pretreatment with tubocurarine chloride diminishes greatly the curarizing effect of a subsequent injection of decamethonium bromide.

Penetration of "Chloromycetin" into the Eye.

IRVING H. LEOPOLD *et alii* (*Archives of Ophthalmology*, July, 1950) have studied the penetration of "Chloromycetin" into the eye following intravenous, oral and local administration. Using rabbits, they found that after intravenous administration there was a fairly high concentration in the aqueous humour in thirty minutes, but by the end of four to six hours little of the active drug was still present. Concentration in the vitreous was not as high as in the aqueous. Detectable concentrations were also found in the cornea, iris, chorio-retinal tissues, sclera, conjunctiva, muscle, and lachrymal gland. After oral administration detectable levels of the drug were found in the aqueous and vitreous for six hours after a single dose. The concentrations were not quite so high as after intravenous administration. Solutions of "Chloromycetin" instilled as drops into the eye penetrated into the anterior chamber, penetration being greater when the cornea was abraded. The same held true for ointments. Cathode iontophoresis produced an increased concentration of "Chloromycetin" in the anterior chamber. When it was injected subconjunctivally definite irritation was produced, and the concentration resulting was not much greater than that which followed use of drops. "Chloromycetin" has many advantages over other antibiotics in that it can be administered orally, after oral administration it will penetrate into the ocular tissues, there are no toxic symptoms following oral administration, and solutions for local use need not be refrigerated, being stable for several weeks at room temperature. The field of activity is about the same as for aureomycin, although aureomycin is more effective against Gram-positive organisms. For oral use the authors suggest three to six grammes daily, the initial dose being three grammes, and then 0·5 gramme every four hours. For local use an aqueous solution of "Chloromycetin" containing 2·5 milligrammes per millilitre is safe, as also is an ointment containing 50 milligrammes per gramme.

Veratrum Viride.

R. W. WILKINS (*The New England Journal of Medicine*, April 6, 1950) reports his observations on *veratrum viride*. He states that the tincture, the aqueous extract and the powder often vary widely in effect. Some reduce blood pressure, others cause

vomiting. Action on the dog seems to parallel that in man. The author gave the drug by mouth for preference after meals. Nausea and vomiting frequently occurred with all preparations. He states that the blood pressure may be reduced too much and cause fainting; persistent trial of small doses is advised. In conclusion, he states that the drug does reduce pressure, that it may cause nausea, vomiting or collapse, and that it is worth further study.

Subacute Bacterial Endocarditis.

C. K. FRIEDBERG (*The Journal of the American Medical Association,* October 14, 1950) discusses the treatment of subacute bacterial endocarditis with newer antibiotics. He states that a high proportion of cures should be anticipated, but figures show that only about 63% to 66% of patients have recovered in recent years. The recovery rate was best in those treated within two months of the onset, and in those in whom the causative organism was found. Treatment was recommended in suspected cases even though the result of blood culture was negative. In such a case treatment should begin with 2,400,000 units of penicillin given daily. If clinical improvement does not appear, larger doses are indicated, until 0·25 unit per millilitre is found in the blood. Thereafter penicillin in large doses should be combined with full doses of aureomycin or dihydrostreptomycin, two to three grammes daily.

Brucellosis.

W. E. HERRELL AND T. E. BARBER (*The Journal of the American Medical Association,* October 14, 1950) describe a new method of treating brucellosis. They state that sulphadiazine, streptomycin and "Chloromycetin" have all given some good results. However, experimentally and clinically the combined use of aureomycin and dihydrostreptomycin gave best results. A dose of 750 milligrammes of aureomycin hydrochloride was given orally every six hours, a total of three grammes per day. At the same time one gramme of dihydrostreptomycin was given intramuscularly every morning and evening. In severe cases this is kept up for fourteen days. Both *Brucella abortus* and *Brucella suis* were found in the series of cases reported by the authors. Twenty-five patients were treated, mainly for bacteriæmic brucellosis. Pulmonary manifestations such as pneumonia responded well to treatment, and the results were equally good with either type of organism.

NEUROLOGY AND PSYCHIATRY.

"Doodling" in Neurotics.

J. G. AUERBACH (*The Journal of Nervous and Mental Disease,* April, 1950) states that during his psychotherapeutic sessions he supplies pencil and paper, so as to encourage his patients to "doodle". He is careful not to suggest the subject. From thousands of "doodles" he gives numerous illustrations, many of which are of considerable artistic excellence. In order of frequency, they deal with the following subjects: the self; ethical, religious and moral problems; sexual problems (these three constantly overlapping); analyst and analysis; innumerable individual problems which defy classification. Trends and conflicts are illustrated in many "doodlings". Frequently there are changes within the hour of observation. The author considers that this is important, as it gives the analyst a valuable warning to change the strategy. He finds that "doodlings" of schizophrenics have special characteristics. Upon occasion the "doodlings" of patients show the progress of the disease in much the same way as the temperature chart illustrates the course of a fever.

Vitamin E.

SIMON STONE (*The Journal of Nervous and Mental Disease,* February, 1950) outlines his treatment with vitamin *E* in diseases of the nervous system. For infants and children cold pressed wheat germ oil was used in a dosage of one to two millilitres per 10 pounds of body weight. For adults natural mixed tocopherols were administered in 50 milligramme capsules, one to three daily. The author claims benefit in a large variety of conditions. He states that in the young it is used with advantage in selected cases of muscle hypotonia and dysplasia, also after anterior poliomyelitis. In cases of congenital non-obstructive hydrocephalus it produced arrest or slowing down of progression of head enlargement. A number of children with progressive hydrocephalus have developed normally after receiving wheat germ oil for varying periods of time. The author considers that it should be tried in all cases of amyotrophic lateral sclerosis in the female. Benefit was obtained in *tabes dorsalis* and multiple sclerosis.

Autistic Thought.

SILVANO ARIETI (*The Journal of Nervous and Mental Disease,* April, 1950) considers that autistic thought is not confined to schizophrenics, but that in some individuals it merely represents a phase in the development of thinking. The average man thinks according to the rules of Aristotelian logic. For example, given the premises "all men are mortal" and "Socrates is a man", it is concluded that Socrates is mortal. In autistic thinking, if told that Indians are swift and stags are swift, there is a conclusion that Indians are stags. The author points out that certain primitive peoples habitually use this principle. He gives two histories in which it occurs in non-schizophrenics, and states that the distinction is important. He bases his concept of palæologic thought on the Von Domarus principle, which he defines in the following terms: "Whereas the normal person accepts identity only upon the basis of identical subjects, the person who thinks autistically accepts identity based upon identical predicates."

Discussion Groups.

A. N. MAYERS (*The Journal of Nervous and Mental Disease,* June, 1950) gives a psychiatric evaluation of discussion groups. He reviews their utility in providing a better understanding of social and other issues. He states that our democracy is challenged by the new methods of communication which enable a few calculating people to enslave millions. The remedy lies in the widespread use of discussion groups. The author considers that they should have optimally not more than 40 members, and not less than five or six. Sessions last from sixty to ninety minutes. Much depends upon the leader, who must be permissive, develop a good counter-transference to the group and guide the relevancy and consistency of the discussion rather than cram information into the members of the group. The excellent results which are obtained are due to a number of causes including emotional catharsis. The author sees a hopeful aspect in the growth of love for the group itself and for the leader. He states that if we do not grow to love each other quickly, we shall undoubtedly kill each other quite rapidly.

Psychosis in Adolescence.

WILFRED WARREN AND KENNETH CAMERON (*The Journal of Mental Science,* April, 1950) state that, in contrast to the general view that psychoses in children have a prolonged course, there may be an acute onset with a stormy course abating in a few weeks; repeated acute phases may result in deterioration. In the prodromal stage a relatively sudden drop of scholastic efficiency and diminished powers of concentration, together with headache and other physical discomforts, may be followed by a turbulent psychotic condition, with acute anxiety, sleep disorder, restlessness, general perplexity, bizarre bodily sensations, hallucinations occasionally, and lack of contact with the environment, lasting a few days. The author investigated six children between the ages of eleven and sixteen years. The precipitating factor was uniform in each case, namely, a separation of the child from its mother, parents or home circle, and a severe psychosexual conflict often related to an undue attachment to the heterosexual parent. The children recovered spontaneously or ultimately made a very good response to psychotherapy.

Electroconvulsive Treatment.

IRVING L. JANIS (*The Journal of Nervous and Mental Disease,* June, 1950) discusses the psychological effects of electroconvulsive treatment. The emotional changes are investigated by a series of standardized interviews, assessed as self-rating scales. These are given before and after the treatment. The results support a general conclusion that there is a reduction in affective disturbance. The author discusses the reasons for the patient's improvement. There is evidence that whilst electroconvulsive treatment produces a direct effect upon the affect or emotion, it seems probable that generalized amnesia is a contributory factor. He states that by partially eliminating from the patient's consciousness a substantial block of memories which tend to arouse intense affect, the post-treatment amnesias may have the effect of reducing certain areas of affective disturbance. In other words, the post-treatment amnesias may be equivalent to a new mode of defence which has an effect similar to "repression" in facilitating the avoidance of disturbing affect. He quotes the case of a man who hated his mother so much that he could not live with her. After electroconvulsive treatment he had forgotten his hostilities and decided to live with her again. Two months later the forgotten memories had returned and he hated her worse than ever.

British Medical Association News.

SCIENTIFIC.

A MEETING of the New South Wales Branch of the British Medical Association was held at the Saint George Hospital, Kogarah, New South Wales, on November 23, 1950. The meeting took the form of a number of clinical demonstrations by members of the medical and surgical staffs of the hospital. Part of the report of this meeting appeared in the issue of December 16, 1950.

Œsophageal Diverticulum.

DR. A. C. THOMAS presented a woman, aged fifty-three years, who complained of "food sticking in her throat" (both solids and liquids) for the past twelve months, and of mucus in the throat which, she stated, stayed for hours; the symptoms were aggravated when she lay on her left side, and she had regurgitation of fluids on bending forwards. She had lost two stone in weight during the previous twelve months. She had often noticed a noise in her throat "like asthma". Physical examination of the patient revealed no abnormality in the neck. X-ray examination with barium bolus showed an œsophageal diverticulum directly in the mid-line above the suprasternal notch projecting down behind the œsophagus for about one inch. An œsophagoscope passed the cricoid constriction and went about two centimetres beyond. At that point a blind end was encountered; presumably the instrument was in the blind pouch. No entry into the main part of the œsophagus could be visualized. One week later, at operation through a linear incision on the right side of the neck, Dr. Thomas found an œsophageal diverticulum on the posterior wall at the back of the inferior thyreoid artery, about half an inch in diameter. He dissected out the sac from the muscles, excised it, sutured the mucous membrane and brought the muscles over the sutured area. The patient had immediate relief of symptoms with no further recurrence.

Hæmangioma of the Liver.

Dr. Thomas's second patient was a young man, aged twenty-two years, who had suffered from a duodenal ulcer for four years. His presenting symptoms were hæmatemesis (he had three times vomited about three-quarters of a pint of dark blood, this, on each occasion, being followed by melæna), epigastric pain (radiating to the back and unrelieved by alkaline powders, present for the past six months), a hard, smooth, non-tender lump under the right costal margin for the past three months, and loss of weight (20 pounds in one year). Dr. Thomas performed a laparotomy, and found a very large, hard left lobe of the liver and a large nodule on the superior surface of the right lobe, small nodules on the surface of the liver, one of which was removed for biopsy, and a duodenal ulcer. Microscopic examination of a section of the nodule showed the presence of tumour foci composed of sheets of fairly uniform polyhedral and short spindle cells, directly walling circulatory paths of various shapes and sizes. The tumour cells were not encapsulated, but were clearly demarcated from the adjacent liver cells. The appearances were those of malignant hæmangioendotheliomata. The pathologist considered that it would be impossible to tell the exact site of origin. The patient was referred for deep X-ray therapy and appeared to have some recession of the growth.

Aberrant Thyreoid.

Dr. Thomas's third patient was a girl, aged fifteen years, who had been admitted to hospital two and a half years before. Her only symptom at that time was a swelling in the right side of the neck which she had noticed for seven months; it had not enlarged in size. She had no difficulty in swallowing nor any cardio-vascular symptoms. At operation, Dr. Thomas excised a small lump in the right side of the neck behind the sterno-mastoid muscle. Microscopic examination revealed a dense fibrous tissue stroma enclosing thyreoid alveoli of varying size containing scattered amounts of colloid. No definite evidence of malignant change was present, but the general pattern of the tumour suggested local invasive capacity after operation. The basal metabolic rate was *plus* 2%. One month later Dr. Thomas performed a right hemithyreoidectomy, and in the lobe removed was found a small cyst. The patient's basal metabolic rate on discharge from hospital was *plus* 5%.

Two years later the patient was again admitted to hospital. She had a soft lump on the right side of the neck under the sterno-mastoid muscle extending from the angle of the jaw to the upper border of the clavicle. At operation the lump was removed; it consisted of five irregular, bluish, semisolid nodules. Microscopic examination showed hyperplastic papillary adenomata of thyreoid tissue surrounded by a thin fibrous capsule; it was similar to the biopsy material of two years previously. One month later a lump was removed together with a few lymph glands. Microscopic examination again revealed aberrant thyreoid tissue with no involvement of the lymph glands. Three months later the patient again returned with another nodule palpable low down on the left side of the neck under the sterno-mastoid muscle. At operation Dr. Thomas removed the left lobe of the thyreoid together with the nodule of abberant thyreoid tissue. After operation the patient's basal metabolic rate was normal.

Cup Arthroplasty.

DR. A. L. WEBB presented a man, aged seventy-three years, who had been admitted to hospital on August 6, 1950, suffering from pain in the left hip joint for twelve months, tiredness of the left leg for three years and limping for eighteen months. At operation on August 8 a condition was found of gross osteoarthritis of the left hip. Cup arthroplasty of the left hip was carried out. On September 27 the patient was walking with the aid of crutches.

Pertrochanteric Fracture of the Femur.

Dr. Webb's second patient, a woman, aged sixty years, had sustained a subcapital fracture of the left femur eleven years previously and had been treated with a Smith-Petersen nail. She had been walking without limp or pain until eighteen weeks before, when she fell on her left hip. X-ray examination showed a pertrochanteric fracture of the femur with the Smith-Petersen nail *in situ*.

Slipped Femoral Epiphysis.

DR. C. P. HUDSON showed a boy, aged thirteen years, who had been admitted to hospital on August 27, 1950. The child's height and weight were excessive. He had been limping for three weeks and examination revealed one inch of shortening of the left leg. X-ray examination showed pronounced slipping of the capital epiphysis of the left femur, the neck being displaced outwards. Hamilton Russell traction was applied for one month. On September 25 osteotomy of the neck of the left femur was carried out with insertion of a Smith-Petersen nail. On November 1 the child was walking with the aid of crutches. A course of testosterone had been commenced.

Kienböck's Disease.

Dr. Hudson's second patient, a man, aged thirty-eight years, had been first examined on February 2, 1950, when he complained of a painful left wrist for four years. Examination revealed tenderness over the dorsum of the wrist with painful limitation of movement, particularly extension. X-ray examination revealed considerable deformity of the lunate bone with compression, fragmentation and sclerosis. The appearance was that of osteochondritis (Kienböck's disease). On November 20 operation was performed for excision of the left lunate bone.

Medical Societies.

MELBOURNE PÆDIATRIC SOCIETY.

A MEETING of the Melbourne Pædiatric Society was held in October, 1950, at the Children's Hospital, Carlton.

Pink Disease.

DR. HOWARD WILLIAMS, DR. W. B. MACDONALD and DR. V. CALLOW presented a paper entitled "Pink Disease: Its Relation to Adrenal Function and the Value of Salt and Desoxycorticosterone in Treatment" (see page 363).

DR. ROBERT SOUTHBY said that he had enjoyed considerably his role as one of the medical observers in the controlled experiment on testing the value of salt and desoxycorticosterone in the treatment of the disease. He felt sure that it was only by observations carried out under circumstances in which the assessor had no knowledge as to which patient was being treated and which one was not, that reliable and unbiased opinion could be obtained. He considered that the close agreement of all observers in their assessment of the progress of the individual patients

was strong proof of the accuracy of their individual assessments and left little doubt as to the validity of the results. In conclusion, he said that there was still a great deal to learn about pink disease, and he wondered what would be the final answer. He was interested to know whether any speaker could give him any help on what appeared to be the epidemic nature of the disease. Groups of cases frequently cropped up in different localities at different times, and this phenomenon suggested that the disease had some underlying infective basis.

PROFESSOR R. D. WRIGHT said that there seemed to be little doubt that salt and desoxycorticosterone treatment was not effective therapeutically in pink disease, even though only ten cases had been used in the experiment. As there was no indication of any significant difference, he considered that there was no point in continuing the observations over a larger series of patients. He wondered whether the administration of large quantities of salt and desoxycorticosterone might not be dangerous to these children, and asked whether the clinical observers had noted any ill-effects from their use. Looking at the phenomena of pink disease, he thought that they were best explained by some disturbance of function of the hypothalamic region of the brain, and thought that it would be well worth while to have an experienced neuroanatomist examine in detail that region of the brain of any infant who died from pink disease.

Dr. Howard Williams thanked both speakers for their remarks, and said that he had no explanation to offer as to why groups of cases of pink disease occurred in different localities at different times. In reply to Professor Wright, he said that so far as he could determine no ill-effects had been noticed from the administration of large quantities of salt and desoxycorticosterone; but he agreed that such a proceeding was therapeutically undesirable and could be dangerous. He agreed with Professor Wright's proposition that the phenomena of pink disease could be best explained as a disturbance of hypothalamic function, and said that he would make an approach to the appropriate neuroanatomist to try to interest him in the problem.

A MEETING of the Melbourne Pædiatric Society was held at the Alfred Hospital, Melbourne, in November, 1950. The meeting took the form of a series of clinical demonstrations by members of the honorary medical and surgical staff of the hospital.

Juvenile Hepatic Cirrhosis.

DR. H. C. COLVILLE showed a boy, aged ten years, who had been quite well until one year previously, when, after an attack of measles, he commenced to become jaundiced. The jaundice steadily increased, and for a period of six months he was under the care of the doctor in the country town in which he lived; during that time it was noted that the child became weak and listless, the liver steadily enlarged, the urine was dark in colour, and the fæces were clay-coloured. At that stage he was admitted to the Alfred Hospital for investigation. During a period of observation the previous findings were confirmed. The liver was very firm and grossly enlarged, reaching well below the umbilicus in the mid-line. The spleen was not palpable. Numerous biochemical investigations were carried out; the main findings were that the urine contained bile pigment and salts and that examination of the blood serum revealed a prothrombin level varying between 50% and 100% and an alkaline phosphatase content averaging 70 units; the result of Hanger's cephalin flocculation test was negative.

After two months of medical treatment no improvement had occurred and the condition was regarded as one of high-grade biliary obstruction. It was decided to perform an exploratory laparotomy, and after pre-operative blood transfusion, that was done on July 6, 1950. It was found that the liver was grossly enlarged, hard, and of fairly smooth surface. The gall-bladder was collapsed, and no bile could be demonstrated in that organ or in the larger bile ducts. The gall-bladder was filled with 15 millilitres of radioopaque fluid, and gently squeezed; X-ray films taken immediately showed that the fluid had passed along the common duct into the duodenum without difficulty. A small piece of the liver was removed for biopsy and the abdomen was closed. The pathologist submitted the following report on the biopsy specimen:

> The liver is very disorganized with no normal lobules to be seen. There are irregular masses of liver parenchymal cells, some of which contain intra-cellular bile. There is very marked bile-duct proliferation in broad masses of fibrous tissue which radiate from the portal tracts. This type of cirrhosis suggests a biliary obstructive condition rather than a primary disease of the parenchyma.

Dr. Colville said that the child's general condition had changed very little in the four months between the operation and the present time. Biochemical findings were largely unaltered, but signs of portal obstruction were gradually developing, namely, ascites, which required paracentesis, and two attacks of hæmatemesis.

Dr. Colville considered that there were a number of lessons to be learned from a careful study of this patient. Although all the evidence pointed to biliary obstruction, he wondered whether the child should have been explored. He said that there seemed to be two different opinions concerning exploration in patients with this particular type of illness. Some Swedish workers had pointed out that in a certain number of patients the mechanical obstruction of the biliary ducts, usually by a mucous plug, was an important factor, and improvement had followed when the lower biliary ducts had been rendered patent by saline irrigation. In contradistinction to that opinion, Perkins, of the Mayo Clinic, had stated that the duct system was normal and the lesion was primarily in the hepatic lobules; surgery was therefore of no value at all. Dr. Colville thought that the prognosis for the child under discussion was poor, as the jaundice was still persisting and he was developing evidence of portal venous obstruction in that ascites was present, there was an anastomatic vascular circulation in the wall of the abdomen, and he had had two attacks of hæmatemesis.

In discussing this patient, DR. PARSONS stated that, although all the clinical and biochemical features were those of obstructive jaundice, yet the pathology was unquestionably one of hepatitis, probably of viral ætiology. He said that the history of the pathology of infective hepatitis was very instructive. The Continental school of pathology had originally regarded the patients as having an ascending infection of the biliary duct system with or without secondary features of infective hepatitis. Study of patients with infective hepatitis during the war led to the view that the disease was primarily one affecting the liver lobule and was therefore a diffuse hepatitis, the duct system not being involved at all. Dr. Parsons thought that the answer, in some patients at least, was that there was a mixture of both hepatitis and catarrhal duct obstruction. Presented again with a patient with clinical features of the type described, he thought that one would have to advise exploratory operation.

DR. IAN WOOD said that in patients of the type presented the diagnosis on clinical and biochemical grounds was uncertain and exploration could be reasonably carried out. The prognosis in the particular boy shown was very uncertain. Although it seemed poor at the time, resolution might proceed and the child might have many years of useful life in front of him, even though considerable scarring with liver cirrhosis had resulted.

An Unusual Pulmonary Lesion.

DR. GUY SPRINGTHORPE presented a patient for diagnosis, a boy, aged six years, who had been first examined at the age of one year and eleven months as a patient in the Alfred Hospital from May 23 to July 13, 1946, with generalized bronchopneumonia. That improved with a full course of sulphadiazine, but consolidation persisted at the right lung base and was unaffected by penicillin. Repeated X-ray examination of the chest showed gradual resolution over the next two months, and although the boy's general condition improved, cough and some bronchial spasm persisted. There was a history at that time of his never being free from colds, and of several attacks of bronchopneumonia since the age of five months. The result of his Mantoux test was negative. Over the remainder of the winter in 1946 he had further recurrent colds with cough and some wheezing and scattered rhonchi on examination. He was sent to the country for three months in the following summer. On returning he developed further colds and also tonsillitis. Chest X-ray examination on May 20, 1947, revealed "bronchitic changes". The history being suggestive of early bronchiectasis, a lipiodol bronchogram was prepared in September, 1947, but it revealed no definite evidence of bronchiectasis. Owing to persistent colds, removal of tonsils and adenoids was advised and carried out in March, 1948. The nasal mucosa appeared allergic, and microscopic examination of the tonsils showed no tubercle bacilli. Three days after tonsillectomy he was readmitted to hospital with cough and temperature of 101·4° F. and some sputum. X-ray examination at that time showed a considerable area of consolidation in the upper lobe of the left lung. At first the possibility of lung abscess was considered, but the cough and pyrexia soon subsided, although the consolidation in

the upper lobe of the left lung was shown by repeated X-ray examination to be extending. At that time the result of the Mantoux test was found to be positive, and culture of gastric contents and a guinea-pig test set up later returned positive evidence of tubercle bacilli in both instances. On that account he was diagnosed as having tuberculosis, and kept in hospital for the next four and a half months, pending transfer to the Austin Hospital. About that time the mother was found also to have pulmonary tuberculosis. The time of onset in her case was uncertain, but the mother stated that a few months previously a chest X-ray examination at the Tuberculosis Bureau had revealed no abnormality. The boy was kept at the Austin Hospital from July, 1948, to December, 1949. X-ray examination on August 4, 1948, showed dulness at the left apex with some retraction, vague mottling in the right infraclavicular region, and slight increase in lung markings generally. The result of gastric culture at that time was negative.

Repeated X-ray films over the next eighteen months showed little change except that the markings in the upper lobe of the left lung diminished. Sinus X-ray films were normal. The patient's general condition on discharge from the Austin Hospital was satisfactory, although his weight had increased only from two stone eleven pounds to three stone one pound. He was readmitted to the Alfred Hospital on September 28, 1950, after a sudden feverish attack, and his temperature was found to be 105° F. However, the temperature fell to normal in two days without chemotherapy. Chest X-ray examination at that time showed the apex of the left lung normal in appearance, but a triangular shadow was present extending outwards from the right hilar region. The results of gastric culture and guinea-pig tests were later reported negative. Repeated X-ray examination over the next seven weeks showed gradual clearing of the right hilar condition.

Dr. Springthorpe said that his patient presented an interesting series of lesions involving the respiratory tract. He thought that in the first place collapse of the right lung had followed a non-specific non-tuberculous infection and that that had resolved slowly. The child had then developed a primary pulmonary tuberculous infection with enlargement of the left hilar glands, together with an associated lesion in the upper lobe of the left lung; that had slowly but steadily resolved, and now all that could be seen was slight enlargement of the left hilar shadow together with some scattered areas of calcification. The child had developed, following the tuberculous infection, an evanescent virus lesion, which had caused infiltration in the region of the hilum.

The Superficial Inguinal Pouch.

DR. MURRAY CLARKE demonstrated in two boys, each aged eight years, the presence of a bilateral superficial inguinal pouch. There was a large space between the fascia of Scarpa and the external oblique muscle, in which the testis was easily palpable and freely mobile. When the testis in one patient was pushed into the inguinal canal it became impalpable. In both patients the testes could be pushed into the scrotum. It was emphasized that the two boys had normal testes, but also rather larger superficial inguinal pouches than usual.

Dr. Clarke said that the presence of the pouches might, at times, make the differential diagnosis between high retractile testes and ectopic testes rather difficult. The palpation of an easily felt mobile testis above the external abdominal ring and lateral to the inguinal canal was not complete evidence of an ectopic testis. It was also difficult at times to differentiate between the undescended and the ectopic testis, when the testis was only a short distance outside the external inguinal ring.

Allowance being made for possible errors in diagnosis on the part of school medical officers, it must be conceded that the work of McCutcheon in Australia, published in 1922 and 1937, and of several others in England, had shown conclusively that the great majority of testes absent from the scrotum in the second year of life would spontaneously descend to the scrotum by the seventeenth year or earlier. In spite of those articles, covering the investigation of more than 8500 boys, categorical statements still appeared in text-books to the effect that only rarely did a testis reach the scrotum on its own initiative after the first year.

While admitting that the ectopic testis required an operation, Dr. Clarke asked whether surgeons were operating too early. Was early operation always a considered action, or had surgeons just drifted into that practice? Actually no well-documented scientific evidence had yet come to hand to show that delay in treating the misplaced testis would result in harm as regards spermatogenetic function or the internal secretion. It should be more widely realized that testicular atrophy occurred after operation in at least 10% of cases, and that figure was a conservative estimate. The course of the atrophy was damage to the blood supply, which was less easy to avoid when the patient was younger and the vessels were more fragile.

In conclusion, Dr. Clarke suggested that more careful investigation might be made of the unsolved problems of spontaneous descent, spermatogenetic function, and the fertility of undescended testes. He considered that until more knowledge was available many cases might well be left to see whether spontaneous descent occurred and surgery could occur as near puberty as possible.

Deaf-Mutism with Partial Blindness.

DR. LAWRENCE STOKES showed a female child, aged nine years and eight months, with deaf-mutism and considerable visual defect from bilateral congenital cataracts almost certainly the result of rubella contracted by the mother early in pregnancy. In addition the child had received no training or education, with the result that she was mentally very underdeveloped. Dr. Stokes said that he was showing the girl as a challenge, to see whether she was capable of being educated, and secondly, if she was, what methods should be used.

The child was the fifth one in the family, the sixth being a mongol, who died in infancy from pneumonia. There were five other children, a healthy younger child and four older children, all of whom were well and had been top of their respective forms at school. During her pregnancy with the child presented the mother had contracted rubella at about the fifth week. At birth it was realized that the baby had congenital bilateral cataracts. One eye was needled when the baby was aged six months, and the second when she was aged eighteen months. Dr. Stokes had first examined the patient at that time, when she was deaf and partially blind.

At the age of four years, the Blind Institute had agreed to take her on trial, but were able to keep her for only a few weeks, as she was very noisy and difficult to handle. She then returned to her home, which was a farm in the Mallee, over 200 miles from Melbourne. Dr. Stokes tried to persuade her mother to let him examine her again in about twelve months' time. The parents, however, considered her condition to be quite hopeless, completely "threw in the sponge", and made no attempt to educate or teach the child. The mother was occupied in caring for her large family, and in her home duties, and as a result no effort was made even to teach the child to feed herself, to dress herself, or to learn by feel the shape of simple objects and animals. After much persuasion, she was brought down to see Dr. Stokes again about eight weeks before the meeting, when she was nine and a half years of age. Examination showed a moderately well-developed child, who had bilateral cataracts and complete deafness. She appeared to be very subnormal. She had very little sight, but when walking about could avoid objects. Her Wassermann test result, electroencephalogram and encephalogram were normal. While she was in Melbourne the Deaf and Dumb Institution took her on probation in their Opportunity Class. After two or three weeks it was felt that she was capable of some education. Dr. Stokes thought that her condition was a real challenge, and that some reasonable attempt should be made to try to help her. She ate well, and during the past few weeks, as a result of much more attention paid to her by her mother, she could now fend for herself a little, and was clean in her habits of micturition and defæcation.

Dr. Stokes said that he had consulted Professor and Dr. Ewing just before they left Australia. In the reply letter Professor Ewing had stated:

> I am afraid that there is only one real expert in modern methods of educating children who are blind and deaf. She is Mrs. Gittzus, of the Perkins Institution for the Blind, Boston, Massachusetts. I believe that your Australian authorities who are concerned with the blind are already in touch with the Perkins Institution. I would suggest that if you wrote to the Director of the Perkins Institution, he is likely to agree to Mrs. Gittzus sending advice to the parents of the patient. Our American friends, who are experts in the education of the deaf, have told us that a number of blind and deaf children have been successfully trained to understand speech through touch, and have learnt to talk well. It is probable that these children all have average and above average ability, but the Perkins Institution will also have had experience with children whose ability is below average.

Dr. Stokes said that he intended to follow that advice.

DR. GUY SPRINGTHORPE said that he considered that there were certain questions one had to answer concerning the patient shown. The first and most important one was an attempt at assessment of her mental potential development. The question one had to attempt to answer was, was the child mentally defective to a greater degree than the defect caused by lack of mental development through deficiency of both hearing and sight? That was an extremely difficult question to answer, as psychometric testing of the child was quite impossible. He thought that she was probably not defective, as she had displayed a relatively normal development of motor function; she had sat up and walked early, and furthermore had walked very well considering that she could not see. The electroencephalogram, the ventriculogram and the encephalogram showed no significant abnormality. In other words, he thought that the child could be educated. The second question was, how could she be educated? As far as he knew the Perkins School at Boston, Massachusetts, was probably the only school that could train such children. Helen Keller had been trained on the lines in use in that school, and he thought that Dr. Stokes was wise in trying to obtain information from the school as to their methods.

DR. RICKARDS agreed that the child presented a very great problem both in assessing whether she could be educated and then in the methods of carrying that out. He said that almost all problems of defective mental development were those consequent on a single defect, such as defective vision, or defective hearing, or emotional starvation, or maldevelopment of some portion of the brain. In the particular child shown the clinician was faced with a double loss of two of the major sensations, namely, vision and hearing. In addition, the patient had also been emotionally starved, as the parents had rejected her and had not carried out any attempt at any sort of education. He agreed with Dr. Springthorpe on the impossibility of using any psychometric method of testing whether the patient could be educated.

Correspondence.

PINK DISEASE.

SIR: In their reports Cheek and Hicks (1950) suggest that pink disease may be due to a failure of the suprarenal cortex to function normally and that the condition is an example of the adaptation syndrome described by Selye.

It is presumed in the adaptation syndrome that there is a failure of the "glycogenic corticoids" to be secreted, whilst the "mineral corticoids" continue to be secreted and to produce a state of relative hyperfunction. However, it has been shown by many workers that the functions of the adrenal steroids are in most cases mixed. The following table taken from Pincus and Thimann (1948) indicates the complexity of their actions.

Substances.	Activity.		
	Mineral.	Diabetogenic.	Anti-Insulin.
Corticosterone	Retention of Na^+.	+++	++
17-hydroxycorticosterone (Compound F).	Excretion of Na^+.	+++	++
17-hydroxy-11-dehydrocorticosterone (Compound E).	Excretion of Na^+.	+++	++
Desoxycorticosterone ..	Retention of Na^+.	Nil	Nil

The urinary excretion of the breakdown products of these steroids has been studied by us in a number of cases of pink disease. Specimens of urine from nine cases of pink disease and from eight control children of the same age group were provided by Dr. Howard Williams, of the Children's Hospital, Melbourne. The technique of Daughaday, Jaffe and Williams (1948) was used to determine the excretion of formaldehydogenic "steroids" in these urines. Crystalline desoxycorticosterone was used as the standard.

The results were as follows:

Excretion of Formaldehydogenic Steroids.
(Milligrammes per Twenty-four Hours.)

Pink Disease.	Controls.
0·36	0·34
0·64	0·36
0·38	0·62
0·40	0·35
0·58	0·37
0·30	0·42
0·63	0·61
0·41	0·52
0·82	—
Mean $0·50 \pm 0·17$[1]	$0·45 \pm 0·12$[1]

[1] Represents standard deviation.

For the two groups N = 15, T = 0·60, and therefore P is 0·5. where T is the variability of the means and P the probability of the result's being entirely due to chance. Therefore there is one chance in two that the difference in these two means is due entirely to chance.

Therefore it can be stated that Cheek's suggestion that pink disease may be due to adrenal failure is not supported by the evidence obtained from the excretion of formaldehydogenic steroids.

However, in view of the mixed functions of these substances and the general lack of precise knowledge of the hormones involved in sodium and potassium metabolism, no conclusion as to the cause of pink disease can be drawn from these experiments.

Yours, etc.,

J. BORNSTEIN.[1]
P. TREWHELLA.[1]

Baker Medical Research Institute,
Alfred Hospital,
Melbourne,
Victoria.

August 22, 1950.

References.

Cheek, Donald B. (1950), "Pink Disease: An Investigation of its Cause and Treatment (Preliminary Report)", THE MEDICAL JOURNAL OF AUSTRALIA, Volume I, page 101.

———, and Hicks, C. Stanton (1950), "Pink Disease or Infantile Acrodynia: Its Nature, Prevention and Cure", *ibidem*, Volume I, page 107.

Daughaday, W. H., Jaffe, H., and Williams, R. H. (1948), "Chemical Assay for 'Cortin'", *The Journal of Clinical Endocrinology*, Volume VIII, page 166.

Pincus, G., and Thimann, K. V. (1948), "The Hormones", Volume I. Academic Press, Incorporated, New York.

THE SCOPE AND TEACHING OF ORTHOPÆDIC SURGERY.

SIR: In your annotation on the development of the specialities in Australia in the last fifty years scant reference is given to orthopædic surgery (THE MEDICAL JOURNAL OF AUSTRALIA, January 6, 1951, page 68). This may be partly because this speciality has not yet received in this country the recognition that it holds in Great Britain and the United States. However, great changes, obvious to all, have occurred. In most hospitals now traumatic cases are kept apart from the general surgical conditions and are treated in special clinics or separate wards and are placed under the care of surgeons who have in turn confined their public and private practice to this speciality.

The field of orthopædic surgery has widened and now comprises a large part of what was once termed general surgery. It has been defined by Sir Robert Jones as "the treatment by manipulation, operation, re-education and rehabilitation of the injuries and diseases of the locomotor system". It originated in the study of deformed children and has come to include not only diseases of bone and joint but also traumatic lesions of the spine and tendons and peripheral nerves. In some of its aspects, such as in the management of chronic arthritis and poliomyelitis, it is more concerned with the prevention of deformity than with actual surgery, and in these and other aspects it is intimately associated with the problems of social medicine.

[1] Working under a full-time grant from the National Health and Medical Research Council.

The teaching of such a large surgical speciality needs revision. At present students are referred for instruction late in their clinical course as if orthopædic surgery was some highly specialized and somewhat rare and difficult subject. In fact it follows most naturally on their basic training in anatomy and would be easily introduced early in their first clinical year. At this stage they should learn how to examine a painful back, a stiff hip or a swollen knee. They can benefit from studying clinical signs, which are more obvious in disorders of the locomotor system than in other parts of the body. They can even understand treatment which is based largely on anatomy and the pathology of repair of bones and tendons and nerves. Moreover, because of the non-operative approach to many problems, a study of orthopædics can be a useful link between the two main divisions of medicine and surgery as usually taught.

At a later stage in their clinical training students should have instruction in the treatment of common fractures, and this instruction should be in proportion to the modern incidence and importance of these injuries. To know how to treat a broken leg should be no less important at the present time than it was to be able to care for a case of lobar pneumonia in a previous decade or even enteric fever at the start of this century. At present often half the surgical beds in the metropolitan hospitals are occupied with traumatic cases, and the number of injuries on the roads and in industry is not likely to grow less. And yet in at least one large teaching hospital students regularly pass out without ever seeing the early treatment of, say, a fractured tibia; without even making a plaster cast or applying a Thomas splint. They are in the same position as a doctor giving his first anæsthetic after reading about it in a book but never having seen a patient anæsthetized.

In the early part of the twentieth century occurred what Sir Harry Platt has called the "abdominal revolution". It has given to this particular brand of surgery an unreal importance which has clouded the teaching of other special branches for many years. New specialities have now developed, and orthopædic surgery, though not new, has greatly widened its scope. In England there are now hospitals devoted to the care of the injured. The value of treating these cases in separate centres was proved in war time and has been confirmed ever since. The teaching hospitals have also enlarged their accident services, and already professorial chairs in orthopædic surgery have been established in London and the provinces. It is likely that we in Australia will follow this lead as we have done in the past, and it is particularly important that the teaching of this branch of surgery should be adjusted to meet these changes.

Yours, etc.,

HUGH C. BARRY.

British Medical Association House,
135 Macquarie Street,
Sydney.
February 19, 1951.

Post-Graduate Work.

THE POST-GRADUATE COMMITTEE IN MEDICINE IN THE UNIVERSITY OF SYDNEY.

Visit of Overseas Lecturer.

THE Post-Graduate Committee in Medicine in the University of Sydney announces the visit to Sydney in April of Dr. William Pickles, M.D., M.R.C.P., Yorkshire general practitioner, who has acquired world fame for his work on the spread of infectious diseases, and for his book on "Epidemiology in Country Practice". Dr. Pickles is visiting Australia at the invitation of the Australian Post-Graduate Federation in Medicine.

Dr. Pickles will take part in the committee's annual general revision course, beginning April 2, 1951, for two weeks, when he will join in a panel discussion on "Problems in General Practice". He will also be taking part in a week-end course to be held at Wagga Wagga on April 14-15, 1951, in conjunction with the Southern Districts Medical Association, and will be visiting Bathurst, Orange and Newcastle.

He will give the following three evening lectures in Sydney, all lectures being held in the Robert H. Todd Assembly Hall, British Medical Association House, 135 Macquarie Street, Sydney, at 8.15 p.m.; admission is by ticket only:

Thursday, April 5: "Epidemiology in Country Practice."
Monday, April 9: "Epidemiology in Country Practice."
Thursday, April 12: "Research in General Practice."

Fee for attendance at the three lectures will be £1 1s., or 10s. 6d. for a single lectures.

Those wishing to apply for tickets are requested to forward remittance to the Course Secretary, the Post-Graduate Committee in Medicine, 131 Macquarie Street, Sydney, as soon as possible, as only a limited number can be made available. Telephones: BU 5238, BW 7483.

THE MELBOURNE PERMANENT POST-GRADUATE COMMITTEE.

PROGRAMME FOR APRIL.

Overseas Lecturer.

DR. WILLIAM PICKLES, general practitioner of Aysgarth, Yorkshire, England, who is famous for his system of charting the spread of infectious diseases and as author of "Epidemiology in Country Practice" and "Research in General Practice", will visit Victoria for two weeks commencing April 16, 1951. His programme of lectures will be as follows:

Monday, April 16: Mooroopna Base Hospital.
Wednesday, April 18: Medical Society Hall, 426 Albert Street, East Melbourne.
Saturday, April 21: Yallourn Hospital.
Thursday, April 26: Medical Society Hall, 426 Albert Street, East Melbourne.
Saturday, April 28: Hamilton Base Hospital.

The subject of the lectures on April 16, 18, 21 and 28 will be "Epidemiology in Country Practice", and on April 26, "Research in General Practice".

All lectures will be at 8.15 p.m., and the fee in each case will be 10s. 6d. per lecture. Resident medical officers of teaching hospitals may attend at half fees, and students and resident medical officers at country hospitals are invited to attend free of charge.

Country Courses.

Mooroopna.

Dr. William Pickles will lecture at Mooroopna on April 16, 1951.

Yallourn.

The following lectures will be given on April 21-22, 1951, at the Yallourn Hospital.

Saturday, 2.30 p.m.: Dr. S. Williams, "The Use of Antibiotics in Diseases of Childhood"; 8 p.m.: Dr. William Pickles, "Epidemiology in Country Practice".
Sunday, 10 a.m.: Dr. J. Devine, "Diagnosis and Surgical Management of Conditions of the Large Bowel"; 2 p.m.: Dr. T. Steel, "Diseases of the Respiratory Tract with Chronic Disability".

The fee for this course is £2 2s., or 10s. 6d. per lecture.

Hamilton.

Dr. William Pickles will lecture at Hamilton on April 28, 1951.

Flinders Naval Depot.

On Wednesday, April 11, 1951, at 2.30 p.m., Dr. Keith C. Bradley will lecture on head injuries at the Flinders Naval Depot. This is by arrangement with the Royal Australian Navy.

Classes Suitable for Candidates for M.D. Part II and M.R.A.C.P.

Thoracic Diseases Course.

A thoracic diseases course will be held under the direction of Dr. Clive Fitts at 2 p.m. on the following dates:

Tuesday, April 3: "The Problem of Indeterminate Lesions of the Lungs", Dr. C. H. Fitts, at the Royal Melbourne Hospital.
Thursday, April 5: To be arranged.
Tuesday, April 10: "Aspects of Pulmonary Tuberculosis", the staff at the Gresswell Sanatorium.
Thursday, April 12: "Surgical Aspects of Non-tuberculous Diseases of the Chest", Dr. J. Hayward and Dr. I. McConchie, at the Royal Melbourne Hospital.

Tuesday, April 17: "Pulmonary Suppuration", Dr. Douglas Gauld, at Prince Henry's Hospital.

Thursday, April 19: "Acute Infections of the Lung", Dr. Eric Clarke, at the Alfred Hospital.

Each lecture will be associated with a demonstration of patients.

The fee for this course is £3 3s., or 10s. 6d. per demonstration.

Pædiatrics Course.

A pædiatrics course, under the direction of Dr. Mostyn L. Powell, will be held at 2 p.m. at the Children's Hospital, Carlton, on the following dates:

Tuesday, April 24: Dr. R. Southby, "Nephritis in Childhood".

Thursday, April 26: Dr. Stanley Williams, "Meningitis in Childhood".

Tuesday, May 1: Dr. M. L. Powell, "Congenital Malformations of the Heart".

Thursday, May 3: Dr. Howard Williams, "Pulmonary Tuberculosis in Childhood".

Tuesday, May 8: Dr. Norman Wettenhall, "Disorders of the Renal Tract in Childhood".

Thursday, May 10: Dr. J. Colebatch, "Malnutrition".

The fee for this course is £3 3s., or 10s. 6d. per demonstration.

Classes for Part I of Higher Degrees and Diplomas.

Classes in physiology, anatomy, pathology and physics which commenced earlier in the year will be continued. Details may be obtained from the Post-Graduate Committee.

Enrolments.

Enrolments for the above courses should be made with the following:

For metropolitan courses: The Secretary, Melbourne Permanent Post-Graduate Committee, 394 Albert Street, East Melbourne. Telephone JM 1547 or JM 1548.

For the Mooroopna lecture: Dr. B. R. Schloeffel, Maude Street, Shepparton. Telephone 67.

For the Yallourn course: Dr. J. M. Andrew, "Burculey", Yallourn. Telephone 228.

For the Hamilton lecture: Dr. S. C. Fitzpatrick, 69 French Street, Hamilton. Telephone 190.

Australian Medical Board Proceedings.

TASMANIA.

THE undermentioned have been registered, pursuant to the provisions of the *Medical Act*, 1918, of Tasmania, as duly qualified medical practitioners:

Apted, John Heath, M.R.C.S. (England), L.R.C.P. (London), 1947, M.B., B.S., 1950 (Univ. London), Queenstown.

Houseman, Gordon, M.R.C.S. (England), L.R.C.P. (London), 1940, D.A., R.C.S. (England), 1946, East Melbourne.

O'Brien, Hubert Desmond, M.B., B.S., 1950 (Univ. Melbourne), Launceston General Hospital, Launceston.

Parkes, Phillip Leonard, M.B., B.S., 1950 (Univ. Melbourne), Launceston General Hospital, Launceston.

McGladdery, Joseph Percy, M.B., B.S., 1936, M.D., D.P.H., 1939 (Univ. London), M.R.C.P. (London), 1947, Launceston.

MacDonald, Colin Bruce, M.B., B.S., 1950 (Univ. Sydney), Launceston General Hospital, Launceston.

McBride, William Griffith, M.B., B.S., 1950 (Univ. Sydney), Launceston General Hospital, Launceston.

Lines, Verlie, M.B., B.S., 1950 (Univ. Sydney), Launceston General Hospital, Launceston.

White, Deniss Howard, M.B., B.S., 1930 (Univ. Sydney), Department of Health, Hobart.

DISEASES NOTIFIED IN EACH STATE AND TERRITORY OF AUSTRALIA FOR THE WEEK ENDED FEBRUARY 10, 1951.[1]

Disease.	New South Wales.	Victoria.	Queensland.	South Australia.[2]	Western Australia.	Tasmania.	Northern Territory.[3]	Australian Capital Territory.	Australia.[2]
Ankylostomiasis	*	..	1(1)	..	..	..	..	..	1
Anthrax	*	..	*	*	..	*	..	..	..
Beriberi	*	*	*	*	*	*	..	*	..
Bilharziasis	*	..	..	..	..	..	..	..	..
Cerebro-spinal Meningitis	3(2)	..	1	..	..	..	..	..	4
Cholera	..	..	..	..	..	..	..	..	..
Coastal Fever(*a*)	*	*	..	*	*	*	*	*	..
Dengue	*	*	*	*	*	*	..	*	..
Diarrhœa (Infantile)	..	..	2(2)	..	..	..	..	..	2
Diphtheria	4(1)	5(5)	2(1)	..	6(4)	..	..	..	17
Dysentery (Amœbic)	*	..	..	..	..	..	..	..	..
Dysentery (Bacillary)	*	1(1)	12(8)	..	1(1)	..	*	..	14
Encephalitis Lethargica	..	..	..	..	..	..	..	..	..
Erysipelas	*	*	*	..	*	*	..	..	..
Filariasis	*	..	..	..	..	..	..	..	..
Helminthiasis	*	..	*	*	*	*	*	*	..
Hydatid	*	..	*	*	..	*	*	..	..
Influenza	*	*	*	..	*	*	..	*	..
Lead Poisoning	*	*	..	*	*	*	*	*	..
Leprosy	..	..	..	..	1	..	..	..	1
Malaria(*b*)	*	..	1	..	..	..	..	..	1
Measles	*	*	*	51(4)	*	*	..	..	51
Plague	..	..	..	..	..	..	..	..	..
Poliomyelitis	73(24)	10(2)	40(2)	19(14)	..	25(10)	..	2	169
Psittacosis	*	..	..	*	*	*	*	*	..
Puerperal Fever	..	..	..	1(1)	..	..	..	..	1
Rubella(*c*)	*	*	..	*	1(1)	*	..	..	1
Scarlet Fever	7(1)	10(5)	7(2)	3(3)	8(7)	1	..	..	36
Smallpox	..	..	..	..	..	..	..	..	..
Tetanus	*	1	1	*	*	*	*	*	2
Trachoma	*	..	*	*	*	*	*	..	..
Tuberculosis(*d*)	22(18)	20(15)	10(7)	11(10)	13(8)	3(1)	..	..	79
Typhoid Fever(*e*)	..	..	..	..	1(1)	..	..	..	1
Typhus (Endemic)(*f*)	..	..	4	..	1(1)	..	..	..	5
Undulant Fever	..	..	2	..	..	..	..	..	2
Weil's Disease(*g*)	*	*	2	*	*	*	*	*	2
Whooping Cough	*	*	*	2(1)	*	*	..	..	2
Yellow Fever	..	..	..	..	..	..	..	..	..

[1] The form of this table is taken from the *Official Year Book of the Commonwealth of Australia*, Number 37, 1946–1947. Figures in parentheses are those for the metropolitan area.

[2] Figures not available.

[3] Figures incomplete owing to absence of returns from the Northern Territory.

* Not notifiable.

(*a*) Includes Mossman and Sarina fevers. (*b*) Mainly relapses among servicemen infected overseas. (*c*) Notifiable disease in Queensland in females aged over fourteen years. (*d*) Includes all forms. (*e*) Includes enteric fever, paratyphoid fevers and other Salmonella infections. (*f*) Includes scrub, murine and tick typhus. (*g*) Includes leptospiroses, Weil's and para-Weil's disease.

Moore, William Mitchell, M.B., B.S., 1948 (Univ. Melbourne), Royal Hobart Hospital, Hobart.
Pitney, Peter, M.B., B.S., 1950 (Univ. Melbourne), Royal Hobart Hospital, Hobart.
Benn, Keith McLeod, M.B., B.S., 1949 (Univ. Melbourne), Scottsdale Hospital.
Caine, Michael Gerald, M.B., B.S., 1950 (Univ. Melbourne), Launceston General Hospital, Launceston.
Fish, Mervyn Thomas, M.B., B.S., 1950 (Univ. Melbourne), Latrobe.

Congresses.

INTERNATIONAL JUBILEE CONGRESS OF THE FRENCH SOCIETY OF GYNÆCOLOGY.

THE International Jubilee Congress of the French Society of Gynæcology, which is being organized by the French Society of Gynæcology in collaboration with UNESCO, will be held in Paris from June 23 to 29, 1951. All requests for information or concerning registration should be made to Dr. Maurice Fabre, Secrétaire Général, 1 rue Jules Lefebvre, Paris (IXe).

Obituary.

CHARLES WILLIAM BRUCE.

WE regret to announce the death of Dr. Charles William Bruce, which occurred on February 27, 1951, at Ulman South, Ulamambri, New South Wales.

Nominations and Elections.

THE undermentioned have applied for election as members of the New South Wales Branch of the British Medical Association:

Killen, John William, M.B., B.S., 1950 (Univ. Sydney), Base Hospital, Tamworth.
Beck, Keith Francis, M.B., B.S., 1950 (Univ. Sydney), Lewisham Hospital, Lewisham.
Chambers, Ross Campbell, M.B., B.S., 1951 (Univ. Sydney), 8 Dobroyd Parade, Haberfield.

The undermentioned have been elected as members of the New South Wales Branch of the British Medical Association:

Monk, Marjorie, M.B., B.S., 1951 (Univ. Sydney), Royal Prince Alfred Hospital, Camperdown.
Nelson, William Paul, M.B., B.S., 1951 (Univ. Sydney), 141 Macquarie Street, Sydney.
Ohlsson, Keithley, M.B., B.S., 1950 (Univ. Sydney), 10 Carnarvon Road, Roseville.
Owen, Francis Septimus, M.B., 1950 (Univ. Sydney), Royal North Shore Hospital, St. Leonards.
Pearce, Maxwell John Morton, M.B., B.S., 1948 (Univ. Sydney), 23 Darling Point Road, Darling Point.
Pennington, Arthur Frederick, M.B., B.S., 1951 (Univ. Sydney), Parramatta District Hospital, Parramatta.
Pringle, Harry Mossman, M.B., B.S., 1951 (Univ. Sydney), Goulburn District Hospital, Goulburn.
Rail, Wilton Whitburn, M.B., B.S., 1941 (Univ. Melbourne), Sheridan Street, Gundagai.
Reid, Bevan Leslie, M.B., B.S., 1951 (Univ. Sydney), Royal Prince Alfred Hospital, Camperdown.
Rivett, Ronald Albert, M.B., B.S., 1951 (Univ. Sydney), 148 Edinburgh Road, Castlecrag.
Sharkey, Bryan Edmund, M.B., B.S., 1951 (Univ. Sydney), Royal Prince Alfred Hospital, Camperdown.
Sharp, Andrew Cruickshanks Fallow, M.B., B.S., 1951 (Univ. Sydney), Inverell District Hospital, Inverell.
Shearman, Rodney Philip, M.B., B.S., 1951 (Univ. Sydney), Royal Prince Alfred Hospital, Camperdown.
Shiels, Eleanor Mary, M.B., B.S., 1951 (Univ. Sydney), Royal Prince Alfred Hospital, Camperdown.
Soper, Henry Lewry, M.B., B.S., 1951 (Univ. Sydney), 9 Tedman Parade, Sylvania.
Swenson, Patricia, M.B., B.S., 1951 (Univ. Sydney), "The Raymond", 68 Elizabeth Bay Road, Elizabeth Bay.
Waugh, Ian Francis, M.B., B.S., 1948 (Univ. Sydney), Princes Highway, Unanderra.
Worling, Babette Josephine, M.B., B.S., 1951 (Univ. Sydney), 2 Eric Road, Artarmon.
Wright, Francis Boyd, M.B., B.S., 1951 (Univ. Sydney), Flat 9, 5 Springfield Avenue, Kings Cross.
Thornton, Sydney Melford, M.B., 1951 (Univ. Sydney), Base Hospital, Wagga Wagga.

Diary for the Month.

MARCH 13.—New South Wales Branch, B.M.A.: Ethics Committee; Medical Politics Committee.
MARCH 15.—New South Wales Branch, B.M.A.: Clinical Meeting.
MARCH 20.—New South Wales Branch, B.M.A.: Council Quarterly.
MARCH 21.—Western Australian Branch, B.M.A.: General Meeting.
MARCH 22.—Victorian Branch, B.M.A.: Executive Meeting.
MARCH 28.—Victorian Branch, B.M.A.: Council Meeting.
MARCH 29.—New South Wales Branch, B.M.A.: Annual Meeting.
MARCH 29.—South Australian Branch, B.M.A.: Branch Meeting.
MARCH 30.—Queensland Branch, British Medical Association: Council Meeting.

Medical Appointments: Important Notice.

MEDICAL PRACTITIONERS are requested not to apply for any appointment mentioned below without having first communicated with the Honorary Secretary of the Branch concerned, or with the Medical Secretary of the British Medical Association, Tavistock Square, London, W.C.1.

New South Wales Branch (Medical Secretary, 135 Macquarie Street, Sydney): All contract practice appointments in New South Wales.

Victorian Branch (Honorary Secretary, Medical Society Hall, East Melbourne): Associated Medical Services Limited; all Institutes or Medical Dispensaries; Australian Prudential Association, Proprietary, Limited; Federal Mutual Medical Benefit Society; Mutual National Provident Club; National Provident Association; Hospital or other appointments outside Victoria.

Queensland Branch (Honorary Secretary, B.M.A. House, 225 Wickham Terrace, Brisbane, B17): Brisbane Associated Friendly Societies' Medical Institute; Bundaberg Medical Institute. Members accepting LODGE appointments and those desiring to accept appointments to any COUNTRY HOSPITAL or position outside Australia are advised, in their own interests, to submit a copy of their Agreement to the Council before signing.

South Australian Branch (Honorary Secretary, 178 North Terrace, Adelaide): All Lodge appointments in South Australia; all Contract Practice appointments in South Australia; Medical Officer, South Australian Railways.

Western Australian Branch (Honorary Secretary, 205 Saint George's Terrace, Perth): Norseman Hospital; all Contract Practice appointments in Western Australia. All government appointments with the exception of those of the Department of Public Health.

Editorial Notices.

MANUSCRIPTS forwarded to the office of this journal cannot under any circumstances be returned. Original articles forwarded for publication are understood to be offered to THE MEDICAL JOURNAL OF AUSTRALIA alone, unless the contrary be stated.

All communications should be addressed to the Editor, THE MEDICAL JOURNAL OF AUSTRALIA, The Printing House, Seamer Street, Glebe, New South Wales. (Telephones: MW 2561-2.)

Members and subscribers are requested to notify the Manager, THE MEDICAL JOURNAL OF AUSTRALIA, Seamer Street, Glebe, New South Wales, without delay, of any irregularity in the delivery of this journal. The management cannot accept any responsibility or recognize any claim arising out of non-receipt of journals unless such notification is received within one month.

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